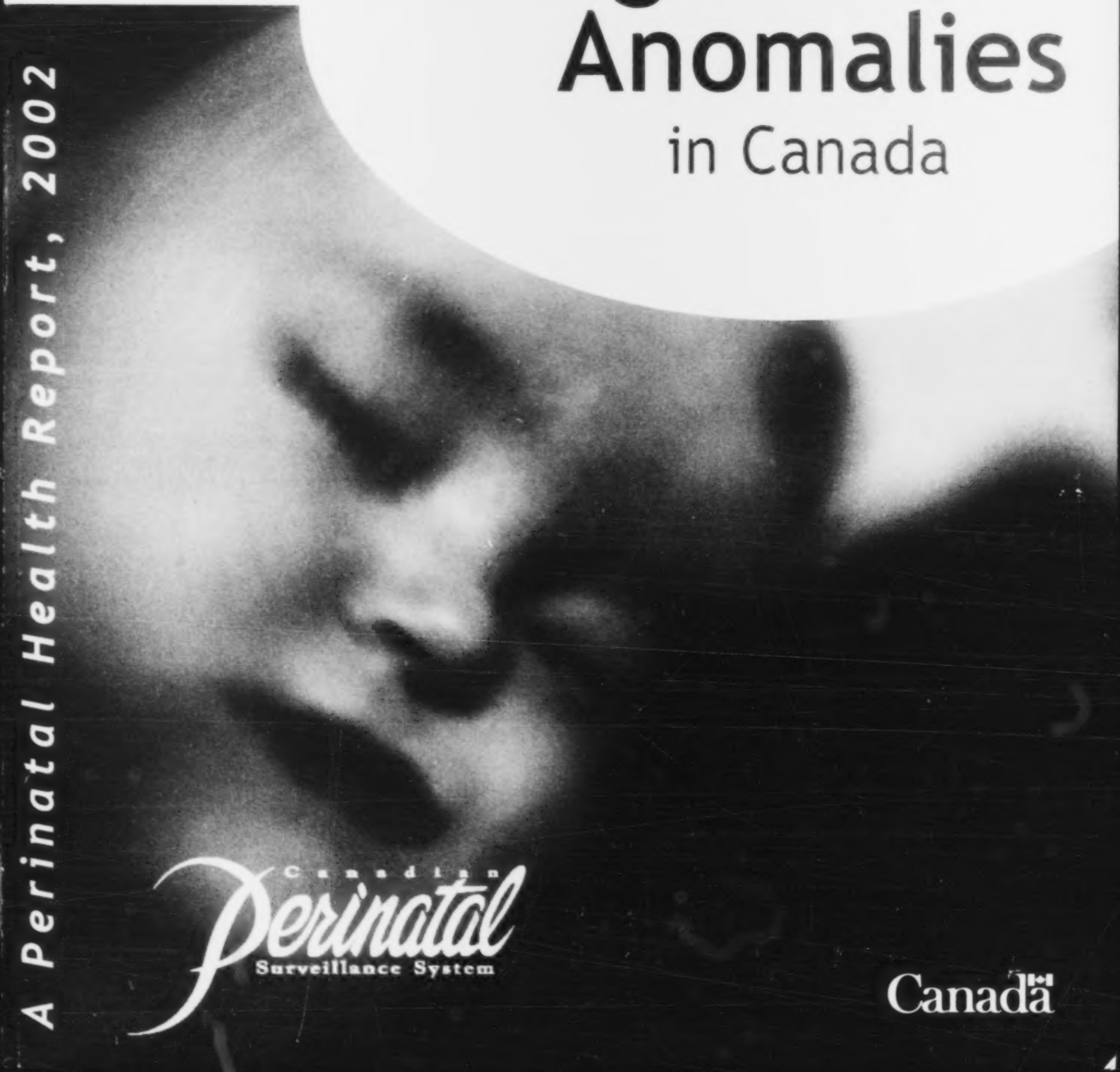
Congenital Anomalies

in Canada

A Perinatal Health Report, 2002



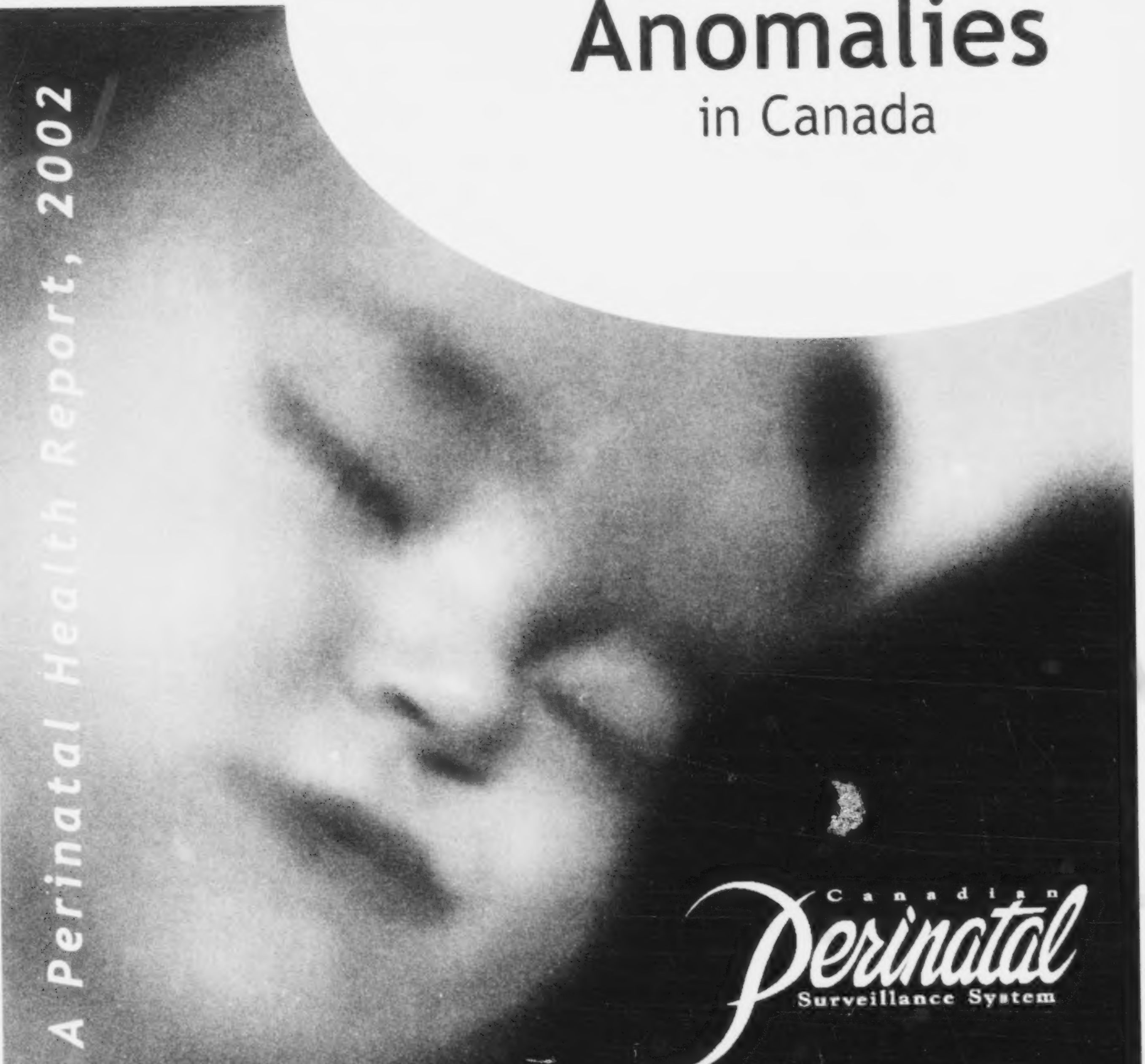
Canadian Perinatal Surveillance System

Canada

103-02330

Congenital Anomalies in Canada

A Perinatal Health Report, 2002



Canadian Perinatal Surveillance System

Our mission is to help the people of Canada
maintain and improve their health.

Health Canada

Copies of this report are available from:

Reproductive Health Section
Division of Health Surveillance and Epidemiology
Centre for Healthy Human Development
Population and Public Health Branch
Health Canada
HPB Bldg. #7, A.L. 0701D
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

Telephone: (613) 941-2395
Fax: (613) 941-9927

This publication can also be accessed electronically via the Internet at:
http://www.hc-sc.gc.ca/pphb-dgspsp/rhs-ssg/index.html

Également disponible en français sous le titre :
Les anomalies congénitales au Canada — Rapport sur la santé périnatale, 2002

Suggested citation: Health Canada. Congenital Anomalies in Canada — A Perinatal Health Report, 2002. Ottawa: Minister of Public Works and Government Services Canada, 2002.

Published by authority of the Minister of Health

©Minister of Public Works and Government Services Canada, 2002
Cat. No. H39-641/2002E
ISBN 0-662-32800-0

Table of Contents

Foreword vii

Contributors ix

Introduction xi

Chapter 1: Down Syndrome (Trisomy 21) 1

- Risk Factors 2
- Prevalence Rate of Down Syndrome in Canada 2
- Provincial and Territorial Prevalence Rates 3
- International Comparisons 4
- Impact of Prenatal Diagnosis on Birth Prevalence of Down Syndrome 4
- Preventive Measures 4
- Summary 5
- References 5

Chapter 2: Neural Tube Defects 7
Risk Factors 7
Prevalence Rate of Neural Tube Defects in Canada 8
Provincial and Territorial Prevalence Rates 9
International Comparisons 9
Impact of Prenatal Diagnosis on Birth Prevalence of Neural Tube Defects 10
Preventive Measures 10
Summary 11
References 11

Chapter 3: Congenital Heart Defects 15
Risk Factors 16
Prevalence Rate of Congenital Heart Defects in Canada 17
Provincial and Territorial Prevalence Rates 18
International Comparisons 18
Impact of Prenatal Diagnosis on Birth Prevalence of Congenital Heart Defects 18
Preventive Measures 19
Summary 19
References 19

Chapter 4: Oral Facial Clefts 21
Risk Factors 21
Prevalence Rate of Oral Facial Clefts in Canada 23
Provincial and Territorial Prevalence Rates 23
International Comparisons 24
Impact of Prenatal Diagnosis on Birth Prevalence of Oral Facial Clefts 24
Preventive Measures 25

Summary 25

References 25

Chapter 5: Limb Reduction Defects 27

Risk Factors 28

Prevalence Rate of Limb Reduction Defects in Canada 29

Provincial and Territorial Prevalence Rates 30

International Comparisons 30

Impact of Prenatal Diagnosis on Birth Prevalence of Limb Reduction Defects 30

Preventive Measures 30

Summary 31

References 31

Chapter 6: Prenatal Testing 35

Prenatal Screening 35

Prenatal Diagnosis 39

Impact of Prenatal Diagnosis on Birth Prevalence of Congenital Anomalies 41

Report on Prenatal Testing Practices in Canada 42

References 42

Bibliography 45

Appendices 55

Appendix A: Data Sources and Methods 55

Appendix B: ICD-9 Codes for Congenital Anomalies Listed in this Report 58

Appendix C: List of Acronyms 59

Appendix D: Data Tables 60

List of Figures and Tables

Figures

Figure 1.1: Down syndrome (DS) rate, Canada (excluding Nova Scotia), 1989-1999 3

Figure 1.2: Down syndrome (DS) rate, by province/territory, Canada, 1997-1999 3

Figure 2.1: Neural tube defect (NTD) rate, Canada (excluding Nova Scotia), 1989-1999 8

Figure 2.2: Neural tube defect (NTD) rate, by province/territory, Canada, 1997-1999 9

Figure 3.1: Congenital heart defect (CHD) rate, Canada (excluding Nova Scotia), 1989-1999 17

Figure 3.2: Hypoplastic left heart syndrome (HLHS) rate, Canada (excluding Nova Scotia), 1989-1999 17

Figure 3.3: Hypoplastic left heart syndrome (HLHS) rate, by province/territory, Canada, 1997-1999 18

Figure 4.1: Cleft lip with or without cleft palate (CL/P) rate, Canada (excluding Nova Scotia), 1989-1999 23

Figure 4.2: Cleft palate (CP) rate, Canada (excluding Nova Scotia), 1989-1999 23

Figure 4.3: Cleft lip with or without cleft palate (CL/P) rate, by province/territory, Canada, 1997-1999 24

Figure 4.4: Cleft palate (CP) rate, by province/territory, Canada, 1997-1999 24

Figure 5.1: Limb reduction defect (LRD) rate, Canada (excluding Nova Scotia), 1989-1999 29

Figure 5.2: Limb reduction defect (LRD) rate, by province/territory, Canada, 1997-1999 30

Tables

Table 1.1: Down syndrome (DS) rate and number of cases, by maternal age, Alberta, 1990-1998 2

Table 1.2: Percent of live births to older mothers (30-39 years), Canada, selected years 2

Table 1.3: Down syndrome (DS) international rate, by country/registry, 1999 4

Table 2.1: Anencephaly and spina bifida international rates, by country/registry, 1999 10

Table 3.1: Congenital heart defect (CHD) rate, by maternal age, California, 1995 16

Table 3.2: Hypoplastic left heart syndrome (HLHS) international rate, by country/registry, 1999 18

Table 4.1: Epidemiology of oral facial clefts 22

Table 4.2: Oral facial clefts international rate, by country/registry, 1999 25

Table 5.1: Limb reduction defect (LRD) international rate, by country/registry, 1999 31

Table 6.1: Summary of prenatal diagnostic tests available in Canada 40

Table 6.2: Proportion of terminations of pregnancy (TOP) among total number of neural tube defect (NTD) cases recorded, by country/registry, 1997-1998 41

Foreword

Congenital anomalies contribute a significant proportion of infant morbidity and mortality, as well as fetal mortality. As a consequence, it is essential to have basic epidemiological information on these anomalies. Initially, in the wake of the thalidomide tragedy of 1958-1962, congenital anomaly registries and/or surveillance systems were set up in the hope that they would detect new teratogens. For the most part, this has not proved successful. One exception is valproic acid, which was identified as a teratogen by Dr. Elisabeth Robert in the Rhône region of France, who noted an association between maternal ingestion of valproic acid and spina bifida. Undoubtedly, a rare defect like thalidomide embryopathy would be ascertained from registry systems because of its unique pattern of anomalies and previously rare occurrence. If a teratogen caused a common anomaly like cleft lip or palate or congenital heart defect, it would be very difficult to pinpoint the cause based on most registry systems. Most teratogenic agents which cause malformations are ascertained by astute clinical observations. Despite the fact that registries will not likely detect a new teratogen, it is of vital importance to collect good statistics to note unusual changes in the baseline rate. If a significant cluster is identified, then an ad hoc investigation should take place. Congenital anomaly rates can also be used for planning health services.

The advent of preventive measures, such as the use of folic acid in the prevention of neural tube defects, has brought a new interest in having good baseline statistics on congenital anomalies. Without these data, it would be very difficult to evaluate the effects of such preventive actions. Folic acid may well be an important agent in preventing other congenital anomalies, such as cleft lip and palate and certain types of congenital heart defects. Prenatal diagnosis followed by selective pregnancy termination will also change the birth prevalence of a number of congenital anomalies; hence the need for registries and surveillance systems to enhance ascertainment of fetal anomalies.

The Canadian Congenital Anomalies Surveillance System (CCASS) was established in 1966, prompted by the thalidomide events. Eight years later, Canada was one of the founding members of the International Clearinghouse for Birth Defects Monitoring Systems

(ICBDMS). Unfortunately, there was a hiatus in CCASS's membership in ICBDMS in the early 1990s, but membership was reinstated in 1996. Currently, CCASS is managed by the Division of Health Surveillance and Epidemiology in the Centre for Healthy Human Development at Health Canada.

In the year 2000, Health Canada brought together participants from all provinces and territories to discuss ways of enhancing the surveillance of congenital anomalies in Canada. In addition to increased reporting of CCASS data, as exemplified by this report, Health Canada agreed to establish and support a formal network for congenital anomalies surveillance. The primary goal of the Canadian Congenital Anomalies Surveillance Network is to increase the quantity and quality of congenital anomalies surveillance activities in Canada. The plan is to develop a working coalition between the various provinces and territories and Health Canada, and to support standardized collection of congenital anomaly data, as well as collaborative surveillance efforts. An important step forward is the development of a website and a newsletter and the production of educational materials. In addition, the first annual scientific meeting of this network will be held in Ottawa in September 2002. As one who has worked in this field for nearly 40 years, I am delighted at the initiative that Health Canada is showing.

R. Brian Lowry, MD, DSc, FRCPC
Medical Consultant
Alberta Congenital Anomalies Surveillance System
Calgary, Alberta

Contributors

Authors

Ruth Kohut, RN, MSc

and

I.D. Rusen, MD, MSc, FRCPC

Division of Health Surveillance and Epidemiology
Centre for Healthy Human Development
Health Canada

Editor

R. Brian Lowry, MD, DSc, FRCPC

Medical Consultant
Alberta Congenital Anomalies Surveillance System
Alberta Children's Hospital

Additional Contribution and Support

Jean-Francois Cayer
Jocelyn Rouleau
Gina Marin
Kathleen Moss, MA
Sharon Bartholomew, MHSc
Susie Dzakpasu, MHSc
Ernesto Delgado

Division of Health Surveillance and Epidemiology
Centre for Healthy Human Development
Health Canada

Acknowledgements

Thank you to Dr. Catherine McCourt and Dr. Reg Sauvé for their valuable comments on the text. The Division of Health Surveillance and Epidemiology also acknowledges the contribution of several organizations that provide data to the Canadian Congenital Anomalies Surveillance System, including:

- Canadian Institute for Health Information
- Statistics Canada
- Système de maintenance et d'exploitation des données pour l'étude de la clientèle hospitalière (Med-Écho)
- Manitoba Health
- Alberta Congenital Anomalies Surveillance System
- Alberta Health and Wellness
- Alberta Vital Statistics

Introduction

Of the approximately 350,000 children born in Canada each year, most are born healthy and at term. However, 2%–3% of these babies will be born with a serious congenital anomaly.[1] More commonly, these babies are born to women with no family history and no known risk factors for congenital anomalies. Infant mortality due to major congenital anomalies has decreased significantly in Canada, from 3.1 per 1,000 live births in 1981 to 1.9 per 1,000 live births in 1995.[2] Nevertheless, major congenital anomalies remain a leading cause of death among Canadian infants in both the neonatal and postneonatal periods. The case fatality rates for the most severe anomalies, such as anencephaly, trisomies 13 and 18, and severe congenital heart defects, are virtually 100% by the child's first birthday.[1] Although less severe birth defects are often correctable, the emotional and economic burden on the family and society is considerable and invariably leaves families and health care providers with unanswered questions regarding the causes, recurrence risks and preventive measures.

A congenital anomaly is an abnormality of structure, function or body metabolism that is present at birth (even if not diagnosed until later in life) and results in physical or mental disability, or is fatal.[3]

A congenital anomaly is considered to be *multifactorial* (or polygenic) in origin when there is a combined influence of (a number of) genes and environmental factors that interfere with normal embryologic development. Multifactorial inheritance is considered when there appears to be a genetic component but there is no clear Mendelian pattern of inheritance. Multifactorial inheritance is the underlying etiology of most of the common congenital anomalies.

Causes of Congenital Anomalies

In spite of the frequency of congenital anomalies, the underlying causes for most remain obscure. It has been estimated that around 15%-25% are due to recognized genetic conditions (chromosome and single gene causes), 8%-12% are due to environmental factors (maternal-related conditions, drug or chemical exposures) and 20%-25% are due to multifactorial inheritance. The majority, 40%-60% of congenital anomalies, have unexplained causes.[4,5]

Genetic causes of congenital anomalies include Mendelian-inherited and chromosomal disorders. In Mendelian-inherited conditions, the child inherits a genetic disease or an at-risk gene from one or both parents, or is affected as a result of a new mutation. Cystic fibrosis, Tay-Sachs disease and hemoglobinopathies are examples of relatively common Mendelian conditions. Chromosome abnormalities, the most common being Down syndrome (DS) or trisomy 21, come about as a result of a change in the number or structure of chromosomes, giving rise to the associated physical and mental problems. When chromosomal disorders and Mendelian inheritance are clinically excluded, most of the common congenital anomalies are believed to be multifactorial in origin, wherein environmental and genetic factors have a joint role in causation.

A teratogen is a factor that has an adverse effect on an embryo or a fetus between fertilization and birth.[6]

The teratogenic risks associated with most maternal environmental exposures are not well-established. Even less understood are the effects of paternal environmental exposures.[7] For the most part, environmental exposures involve multiple agents and other confounding elements, creating difficulty in identifying the underlying cause(s). The essential principles for determining a cause and effect relationship between environmental exposures and congenital anomalies are: an assessment of the strength of the association; evidence for biologic credibility; consistency of the findings with other studies; specificity of the association; and evidence of both time-exposure and dose-response relationships.[8] Proving an exposure is teratogenic requires well-designed epidemiologic research using high quality population-based surveillance data.

Examples of infectious agents that can be transmitted to the fetus and have an adverse effect include rubella, cytomegalovirus, varicella and toxoplasma. A number of drugs have clearly been shown to be teratogenic. The global epidemic of thalidomide-induced limb defects seen in the 1960s resulted in today's practice of monitoring for congenital anomalies worldwide. Other examples of teratogenic agents include folic acid antagonists, anticonvulsants (Dilantin, Tegretol), coumarin derivatives and retinoids (Accutane). The most commonly used teratogenic agent is alcohol. Fetal alcohol syndrome (FAS) has been recognized in Canada as one of the leading causes of preventable birth defects and developmental delay in children.[9,10] A wide spectrum of effects of alcohol on the fetus has been demonstrated. Although these relationships are not fully understood, the magnitude of the risk and the nature of harm to the fetus are dependent on the amount of alcohol intake, the gestational age at exposure and the maternal/fetal genetic predisposition. An estimate of the incidence of fetal alcohol syndrome is 1:1,000 births.[11]

Despite public concerns regarding exposures from the physical environment, actual evidence for the human teratogenic effects from these exposures is limited. Recent research has reported increased risks for structural birth defects and chromosomal abnormalities with air pollution and proximity to hazardous waste sites, respectively;[12,13] however, further studies are required to interpret these findings. Other physical environmental factors with inconclusive findings include maternal pesticide exposure,[14] trihalomethane by-products in public water supplies,[15,16] and industrial areas heavily polluted with lead.[17]

Maternal age is a risk factor for congenital anomalies, specifically chromosome problems. Maternal health conditions that contribute to increased risks for congenital anomalies include obesity, epilepsy controlled with anticonvulsant medications, and insulin-dependent diabetes. More recent but somewhat contradictory research has implicated maternal thyroid disease, even when treated, as increasing the risk for congenital anomaly-affected pregnancies.[18]

Prevention of Congenital Anomalies

Reducing the birth prevalence and associated infant mortality and morbidity attributed to congenital anomalies in Canada is an attainable goal. Primary preventive efforts are clearly the optimal approach for ensuring the healthiest possible pregnancy outcomes for Canadian women. Food fortification with folic acid, promoting folic acid-containing multivitamin use in the periconceptional period, pre-pregnancy immunization against rubella, and interventions to reduce alcohol and drug use in pregnancy are examples of important primary preventive efforts.

Prenatal diagnosis and subsequent termination of affected pregnancies, as well as in-utero treatment of prenatally detected congenital anomalies, are two secondary preventive strategies. As the scope of in-utero treatment remains limited, secondary prevention is mainly achieved through selective abortion. Prenatal diagnosis also contributes to tertiary prevention in cases where an early prenatal diagnosis improves postnatal management and reduces or avoids neonatal complications. Advances in prenatal testing in Canada are presented in detail in chapter 6 of this report.

Surveillance of Congenital Anomalies in Canada

Accurate surveillance contributes to our knowledge of the possible causative factors and impact of preventive measures on the burden of congenital anomalies in Canada.

Uses of Congenital Anomalies Surveillance Data

- to provide accurate data on the burden of congenital anomalies in Canada
- to track trends and identify significant temporal or geographic variation in the occurrence of congenital anomalies
- to evaluate preventive measures
- to provide the evidence base for maternal health program and policy development

Canadian Congenital Anomalies Surveillance System

The Canadian Congenital Anomalies Surveillance System (CCASS) is an essential component of congenital anomaly surveillance in Canada. Established by Health Canada in 1966, CCASS was a founding member of the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS). This database is managed by the Division of Health Surveillance and Epidemiology in the Centre for Healthy Human Development at Health Canada. CCASS provides birth prevalence rates for selected congenital anomalies in Canada. Live births up to one year of age, and registered stillbirths are captured by CCASS. Data are primarily collected from the Canadian Institute for Health Information (CIHI) acute in-patient abstract file "Discharge Abstract Database" (DAD). Manitoba and Québec submit data to Health Canada from systems similar to the DAD — the Manitoba hospitalization database and Système de maintenance et d'exploitation des données pour l'étude de la clientèle hospitalière (Med-Écho), respectively. Data from Alberta come from the Alberta Congenital Anomalies Surveillance System (ACASS). (See Appendix A for a description of the data sources.) CCASS data are coded according to the International Classification of Diseases, Ninth Edition (ICD-9).

> The birth prevalence of congenital anomalies is defined as the number of individual live born and stillborn infants with the congenital anomaly in question (in the numerator), expressed as a proportion of the total number of live births and stillbirths (in the denominator), in a given place and time.
>
> "Birth prevalence" is used rather than "incidence," as affected pregnancies that end in early spontaneous abortion or pregnancy termination are not captured.

Strengths and limitations of Canadian Congenital Anomalies Surveillance System data

CCASS is the only ongoing population-based congenital anomaly surveillance database that is able to estimate the Canadian birth prevalence of specific congenital anomalies. CCASS also provides temporal trends at the national level, in addition to provincial/territorial and international comparisons.

One of the most significant limitations is the inability to monitor the impact of prenatal diagnosis on the birth prevalence of selected congenital anomalies. Affected pregnancies that are terminated prior to meeting the jurisdictional criteria for a stillbirth are not captured in CCASS data. This directly limits an assessment of primary and secondary preventive strategies. Further strengths and limitations of CCASS are outlined in Appendix A.

Provincial and Territorial Congenital Anomalies Surveillance Activities

Alberta Congenital Anomalies Surveillance System (ACASS)

ACASS was first established in 1966 as the Registry for Handicapped Children in Alberta, along with similar systems in British Columbia, Manitoba and New Brunswick. In 1980, it was reorganized as a surveillance system for congenital anomalies of infants born in the province of Alberta. ACASS captures cases from early in pregnancy up to 1 year of age using multiple sources of data for case ascertainment. (A database containing pregnancy terminations for the indication of congenital anomalies has been in operation since 1997.) Although this program is considered a passive system, a medical consultant is available to review questionable diagnoses and actively pursue a confirmation of diagnosis from the ascertainment source or attending physician. ACASS regularly publishes a report (*Alberta Congenital Anomalies Surveillance System Report*), with support from Alberta Health and Wellness, Health Surveillance and Alberta Vital Statistics. ACASS is also an associate member of ICBDMS.

British Columbia Health Status Registry

The Health Status Registry (HSR) in British Columbia operates an independent comprehensive database on congenital anomalies, other genetic conditions, as well as selected disabilities and handicapping conditions. First established in 1952 as the Crippled Children's Registry, the name was changed to the Health Status Registry in 1992 with a legal mandate under the *Health Act*. The HSR is managed by the British Columbia Vital Statistics Agency. Ascertainment of cases is done through multiple sources and registration is not age limited; however, registration of persons with selected disabilities and specific handicapping conditions is limited to those under 20 years of age. Within the HSR, procedures for registering medically terminated pregnancies due to congenital anomalies began in late 1998, with ongoing efforts to improve provincial ascertainment of this information. A regular congenital anomalies report based on the HSR is published annually, providing statistics on more than a dozen specific categories of congenital anomalies by health region. About 9,000 new cases with more than 12,000 diagnoses are reported annually. At the end of 2001, HSR had a total caseload of approximately 215,000. British Columbia is a full member in ICBDMS.

Reproductive Care Program of Nova Scotia

The Reproductive Care Program of Nova Scotia manages the Nova Scotia Atlee Perinatal Database (NSAPD) which contains population-based data from 1988 onwards. Variables include maternal and infant demographics, and information about procedures, interventions, diagnoses and outcomes for women and newborns. The NSAPD is used for ongoing clinical audit, peer review, surveillance, and epidemiologic and clinical research. The Reproductive Care Program reports on a number of variables related to perinatal care and perinatal outcome, including the birth prevalence of congenital anomalies in live births and stillbirths within the province.

In addition to the NSAPD, a fetal anomalies database established in 1992 is managed by the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynaecology, IWK Grace Health Centre. This database captures all pregnancies with a prenatally diagnosed fetal anomaly referred to the centre from Nova Scotia, Prince Edward Island or New Brunswick.

Other provincial programs

In addition to these established provincial systems, plans are also under way for a pilot study of congenital anomaly data collection in Ontario. At one time, Manitoba also had a congenital anomaly surveillance program but, due to difficulties with funding, the program was unable to maintain its infrastructure. However, interest remains strong in re-establishing Manitoba's provincial surveillance system.

Surveillance of exposures related to congenital anomalies

Many regional maternal and prenatal genetic centres across Canada offer information and guidance to pregnant women and their health care providers regarding the potential teratogenic risks associated with a specific exposure in question. The Motherisk program, a multidisciplinary centre affiliated with the University of Toronto, is renowned for its work in the field of teratology. The program's mandate is to provide authoritative evidence-based information on drug, chemical, infection, disease and radiation exposure(s) during pregnancy. A similar program, Info-médicaments en allaitement et grossesse (IMAGe), which is designed to provide health professionals with teratogen risk information, is operated by the Hôpital Ste-Justine in Montréal.

Greater integration of teratology and other exposure databases with congenital anomalies surveillance databases is required. To that end, the Centre for Surveillance Coordination (CSC) in Health Canada has recently become a partner with these two teratogen information services in a pilot project called MotherNet. The proposed system would include a minimum dataset of risk variables, including maternal health and exposures, and pregnancy outcome variables.

The National Children's Study

The National Institute of Child Health and Human Development, along with a consortium of federal agencies in the United States, has been authorized agencies in the United States, has been authorized to conduct a 21-year longitudinal study to "investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes."[19] Background information is available through the National Institute of Child Health and Human Development web page. A database has been prepared for the analysis of determinants of congenital anomalies. As the study is intended to include 100,000 children, following them during prenatal development, through birth, childhood and on into adulthood, it may provide further insight into the etiologies of the more common congenital anomalies.

New initiatives in the Canadian surveillance of congenital anomalies

In May 2000, Health Canada held a national workshop on the surveillance of congenital anomalies with key stakeholders from the provinces and territories, as well as a number of international congenital anomalies surveillance experts. This workshop presented an update on current Canadian congenital anomaly surveillance activities and provided a forum for discussion of provincial and territorial initiatives and issues relating to congenital anomaly surveillance. From the discussions at the workshop, a number of tasks appropriate to the federal level were identified. One such task was to produce a congenital anomalies surveillance report that would highlight this important issue in the Canadian setting. An additional important federal role identified at the workshop was to support a formal network of provinces, territories and other stakeholders to enhance congenital anomaly surveillance at all levels in Canada. Health Canada will formally launch the Canadian Congenital Anomalies Surveillance Network (CCASN) in the fall of 2002. The goals of the CCASN will include:

- increasing the quantity and quality of congenital anomalies surveillance activities in Canada
- developing minimum data sets and common definitions in order to attain quality and consistency in surveillance activities in Canada
- being a resource for professional support — e.g., epidemiology, medical genetics and others — for new and developing surveillance activities
- facilitating collaborative congenital anomalies surveillance and research efforts among provinces and territories
- facilitating the communication of information related to congenital anomalies for both health professionals and the Canadian public
- fostering educational opportunities in congenital anomalies surveillance and research

More information about the CCASN is available at http://www.hc-sc.gc.ca/pphb-dgspsp/rhs-ssg/index.html

Outline of the Report

Congenital Anomalies in Canada provides a concise overview of five important categories of congenital anomalies in Canada. Background information on each category is followed by a review of the known risk factors, national-level birth prevalence data, and provincial/territorial and international comparisons. The impact of prenatal diagnosis on the surveillance of the specific anomalies and prevention opportunities are also discussed. The final chapter of the report is devoted to the important topic of prenatal testing in Canada. This report will provide readers with an appreciation of the burden of specific congenital anomalies, as well as the importance of accurate surveillance in addressing this issue in Canada.

References

1. Harper PS. *Practical Genetic Counselling*, 5th Edition. Boston: Butterworth Heinemann, 1998: 11, 56-70.
2. Wen SW, Liu S, Marcoux S, Fowler D. Uses and limitations of routine hospital admission/separation records for perinatal surveillance. *Chron Dis Can* 1997; 18: 113-9.
3. March of Dimes Resource Center. *Birth Defects*. 1998. (Available www.modimes.org).
4. Stevenson RE. The Genetic Basis of Human Anomalies. In: Stevenson RE, Hall JG, Goodman RM (Eds.), *Human Malformations and Related Anomalies*. Vol. 1. New York: Oxford University Press, 1993: 115.
5. Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. *N Eng J Med* 1984; 320: 19-23.
6. O'Rahilly R, Muller F. Teratology. In: *Human Embryology and Teratology*, 2nd Edition. Toronto: Wiley-Liss Publications, 1996: 110.
7. Trasler JM, Doerksen T. Teratogen update: Paternal exposures-reproductive risks. *Teratology* 1999; 60: 161-72.
8. Hennekens CH, Buring J. Statistical Association. In: Mayrent SL (Ed.), *Epidemiology in Medicine*. Toronto: Little, Brown and Company, 1987: 39-51.
9. Canadian Centre on Substance Abuse. *Joint Statement: Prevention of Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE) in Canada*. 1996. (Available: www.ccsa.ca/fasis/fassmnt.htm).
10. Reprotox: An Information System on Environmental Hazards to Human Reproduction and Development. Alcohol, RTC 1127. 2001. (Available: http://reprotox.org/).
11. Jones KL. *Smith's Recognizable Patterns of Human Malformation*, 5th Edition. Toronto: W.B. Saunders Company, 1997: 555-7.
12. Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. Ambient air pollution and risk of birth defects in Southern California. *Am J Epidemiol* 2002; 155: 17-25.
13. Vrijheid M et al. Chromosomal congenital anomalies and residence near hazardous waste landfill sites. *Lancet* 2002; 359: 320-2.
14. Shaw GM, Wasserman CR, O'Malley CD, Nelson V, Jackson RJ. Maternal pesticide exposure from multiple sources and selected congenital anomalies. *Epidemiology* 1999; 10: 60-6.
15. Dodds L, King WD. Relation between trihalomethane compounds and birth defects. *Occup Environ Med* 2001; 7: 443-6.
16. Graves CG, Matanoski GM, Tardiff RG. Weight of evidence for an association between adverse reproductive effects and exposure to disinfection by-products: a critical review. *Regul Toxicol Pharmacol* 2001; 2: 103-24.
17. Vinceti M et al. Risk of birth defects in a population exposed to environmental lead pollution. *Sci Total Environ* 2001; 278: 23-30.
18. Wolfberg AJ, Nagey DA. Thyroid disease during pregnancy and subsequent congenital anomalies, Abstract #274. Society for Maternal-Fetal Medicine Annual Meeting, New Orleans, 2002.
19. National Institute of Child Health and Human Development. *The National Children's Study*. 2002. (Available: http://nationalchildrensstudy.gov/about/overview.cfm).

Down Syndrome
(Trisomy 21)

Down syndrome (DS) is one of the most common congenital anomalies, occurring in approximately 1 in 800 live births.[1] This chromosome abnormality is characterized by distinctive clinical features, including developmental delay, characteristic facies and associated health problems.

With advances in medical and surgical care, dramatic improvements have been observed in both infant and early childhood mortality and morbidity, as well as in the overall life expectancy of people with DS. Survival through the first year of life for infants with DS born between 1980 and 1996 was over 90%. It is expected that 85% of these affected infants will survive beyond 10 years of age.[2] In 1997, the median age of death calculated from death certificates for people in the United States with DS was 49 years.[3]

Although severe mental handicap is rare, DS causes varying degrees of intellectual impairment. Adults with DS require dependent living conditions and, by the time they reach their late 40s, many develop neuropathological changes characteristic of Alzheimer disease.[4]

Trisomy 21, more commonly known as Down syndrome, occurs as a result of an error in cell division known as *nondisjunction*. This event involves the 21st chromosome pair and occurs during the production of the egg (and less commonly in the sperm) or in early mitosis following conception. Nondisjunction of the 21st chromosome pair gives rise to a conception carrying 47 chromosomes (three copies of chromosome 21 instead of two). A small number of cases of DS arise as a result of *somatic mosaicism* (a proportion of cells has the normal complement of 46 chromosomes and the remaining cells have an extra chromosome 21) or result from an *unbalanced translocation* involving chromosome 21.

2 4

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

Micromedia
ProQuest

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

Children with DS are also at increased risk for other congenital malformations. Approximately 40% are born with a congenital heart defect, particularly of the atrioventricular canal.[5] Although survival in DS infants with congenital heart defects has improved, the presence of a heart defect is still a strong predictor of mortality.[3,6] Individuals with DS are also at risk for gastrointestinal tract obstruction, hypothyroidism, cataracts and conductive hearing deficits. In addition, children with DS have a risk of leukemia 10 to 20 times greater than that of the general population.[5,7] However, ongoing multidisciplinary follow-up and early intervention can minimize the potential secondary medical complications often seen in individuals with DS.

Risk Factors

The only well-established risk factor for DS is advanced maternal age.[1,8] As a woman's age increases, the risk for having a baby with DS also increases. Paternal age, on the other hand, is not a risk factor. Couples with one previously affected child or pregnancy are predisposed to nondisjunction in subsequent pregnancies. The recurrence risk for these couples is approximately 1%.[1,8]

The Alberta Congenital Anomaly Surveillance System (ACASS) stratified the provincial DS rates by maternal age. Table 1.1 illustrates the effect of maternal age on the prevalence rate of DS. In 1990-1998, the birth prevalence of DS for women aged 25 to 29 years was 7.2 per 10,000 total births, compared to 28.3 per 10,000 total births for women aged 35 to 39 years. Furthermore, maternal age at delivery has increased dramatically in Canada in recent years (Table 1.2).[9]

Table 1.1

Down syndrome (DS) rate* and number of cases, by maternal age, *Alberta, 1990-1998***

Maternal age (years)	Rate of DS	Number of cases of DS
< 20	4.8	13
20-24	6.7	51
25-29	7.2	86
30-34	12.7	126
35-39	28.3	98
40-44	63.0	28
> 45	428.6	6

Source: Alberta Congenital Anomalies Surveillance System, 1990-1998.
*Per 10,000 total births.
**Combined rate for the eight-year period 1990-1998.

Table 1.2

Percent of live births to older mothers (30-39 years), *Canada, selected years*

Maternal age (years)	% of live births		
	1980	1990	1995
30-34	17.6	25.9	30.4
35-39	3.9	7.8	10.8

Source: Health Canada, 2000.[9]

The search for specific environmental risk factors has yielded few definitive results.[10] The epidemiologic evidence for an association between exposure to ionizing and non-ionizing radiation[11] and prenatal cigarette smoking[12,13] and DS is inconclusive. Other factors have shown no consistent effect on the occurrence of DS; these include use of oral contraceptives, multiparity, a short time interval between pregnancies and abnormal folate metabolism due to a mutation in the methylene tetrahydrofolate reductase (MTHFR) gene.[14]

Prevalence Rate of Down Syndrome in Canada

There were 487 infants born with DS in Canada in 1999 (all provinces and territories included), corresponding to a birth prevalence of 14.4 per 10,000 total births. As depicted in Figure 1.1 (see also Appendix D, Data Table D1.1), the prevalence rate for the years 1989-1999 for Canada (excluding Nova Scotia) was relatively constant at an average of 13.2 per 10,000 total births (no statistically significant trend). The constant rate over this past decade may in part be due to the opposing effects of two factors — advancing maternal age and increasing utilization of prenatal diagnosis.

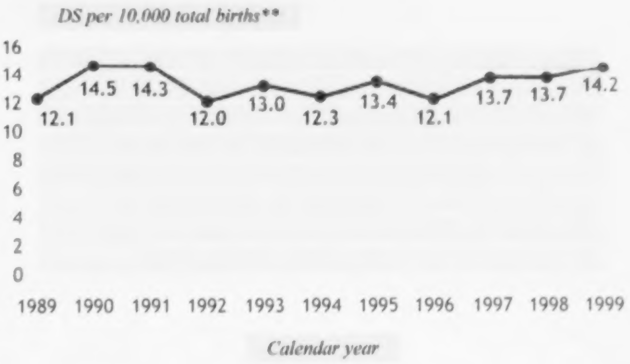
Provincial and Territorial Prevalence Rates

The prevalence rates for the combined three years 1997-1999 are shown in Figure 1.2 (see also Appendix D, Data Table D1.2). Although there appears to be considerable variation between the provinces and territories, the small number of cases and the large confidence intervals in the less populated provinces/territories (such as Prince Edward Island, Yukon and the Northwest Territories) must be taken into account when interpreting these rates. Variation in maternal age, as well as access to or utilization of prenatal diagnosis within a given province or territory, may explain some of the observed differences.

British Columbia, for example, has a high proportion of deliveries by women aged 35 years or older (18.1% of hospital deliveries) and a comparatively high birth prevalence of DS (16.9 per 10,000 total births), whereby the converse is observed in Newfoundland (10.1% of hospital deliveries by women aged 35 years or older and a birth prevalence of DS of 12.9 per 10,000 total births). The proportion of hospital deliveries by women aged 35 years or older within the provinces and territories is presented in Appendix D, Data Table D1.2. CCASS is unable to standardize birth prevalence rates by maternal age or to explore the issue of access and utilization of prenatal diagnosis among the provinces and territories and how this relates to the birth prevalence of DS.

Figure 1.1

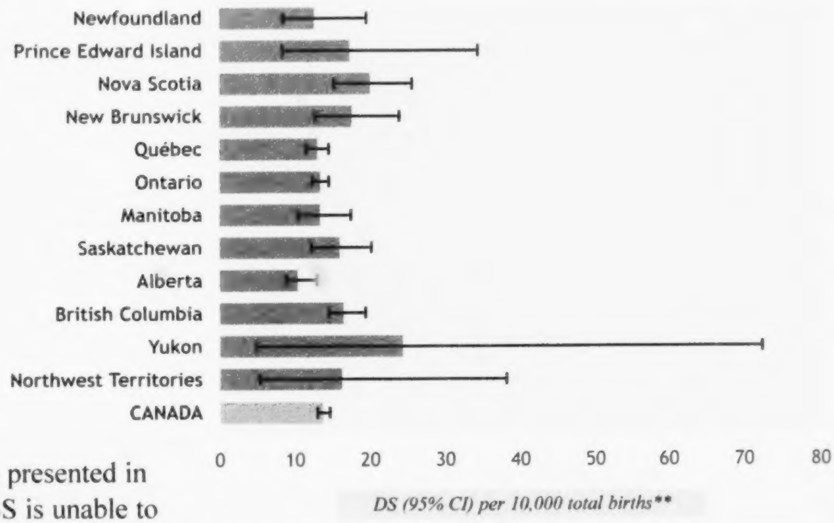
Down syndrome (DS) rate,
Canada (excluding Nova Scotia), 1989-1999*



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.
*Nova Scotia is excluded because data are not available for all years.
**Total births include live births and stillbirths.

Figure 1.2

Down syndrome (DS) rate, by province/territory,
*Canada, 1997-1999**



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.
*Combined rate for the three-year period 1997-1999.
**Total births include live births and stillbirths.
CI – confidence interval.

Children with DS are also at increased risk for other congenital malformations. Approximately 40% are born with a congenital heart defect, particularly of the atrioventricular canal.[5] Although survival in DS infants with congenital heart defects has improved, the presence of a heart defect is still a strong predictor of mortality.[5,6] Individuals with DS are also at risk for gastrointestinal tract obstruction, hypothyroidism, cataracts and conductive hearing deficits. In addition, children with DS have a risk of leukemia 10 to 20 times greater than that of the general population.[5,7] However, ongoing multidisciplinary follow-up and early intervention can minimize the potential secondary medical complications often seen in individuals with DS.

Risk Factors

The only well-established risk factor for DS is advanced maternal age.[1,8] As a woman's age increases, the risk for having a baby with DS also increases. Paternal age, on the other hand, is not a risk factor. Couples with one previously affected child or pregnancy are predisposed to nondisjunction in subsequent pregnancies. The recurrence risk for these couples is approximately 1%.[1,8]

The Alberta Congenital Anomaly Surveillance System (ACASS) stratified the provincial DS rates by maternal age. Table 1.1 illustrates the effect of maternal age on the prevalence rate of DS. In 1990-1998, the birth prevalence of DS for women aged 25 to 29 years was 7.2 per 10,000 total births, compared to 28.3 per 10,000 total births for women aged 35 to 39 years. Furthermore, maternal age at delivery has increased dramatically in Canada in recent years (Table 1.2).[9]

Table 1.1

Down syndrome (DS) rate* and number of cases, by maternal age, *Alberta, 1990-1998***

Maternal age (years)	Rate of DS	Number of cases of DS
< 20	4.8	13
20-24	6.7	51
25-29	7.2	86
30-34	12.7	126
35-39	28.3	98
40-44	63.0	28
> 45	428.6	6

Source: Alberta Congenital Anomalies Surveillance System, 1990-1998.

*Per 10,000 total births.

**Combined rate for the eight-year period 1990-1998.

Table 1.2

Percent of live births to older mothers (30-39 years), *Canada, selected years*

Maternal age (years)	% of live births		
	1980	1990	1995
30-34	17.6	25.9	30.4
35-39	3.9	7.8	10.8

Source: Health Canada, 2000.[9]

The search for specific environmental risk factors has yielded few definitive results.[10] The epidemiologic evidence for an association between exposure to ionizing and non-ionizing radiation[11] and prenatal cigarette smoking[12,13] and DS is inconclusive. Other factors have shown no consistent effect on the occurrence of DS; these include use of oral contraceptives, multiparity, a short time interval between pregnancies and abnormal folate metabolism due to a mutation in the methylene tetrahydrofolate reductase (MTHFR) gene.[14]

Prevalence Rate of Down Syndrome in Canada

There were 487 infants born with DS in Canada in 1999 (all provinces and territories included), corresponding to a birth prevalence of 14.4 per 10,000 total births. As depicted in Figure 1.1 (see also Appendix D, Data Table D1.1), the prevalence rate for the years 1989-1999 for Canada (excluding Nova Scotia) was relatively constant at an average of 13.2 per 10,000 total births (no statistically significant trend). The constant rate over this past decade may in part be due to the opposing effects of two factors — advancing maternal age and increasing utilization of prenatal diagnosis.

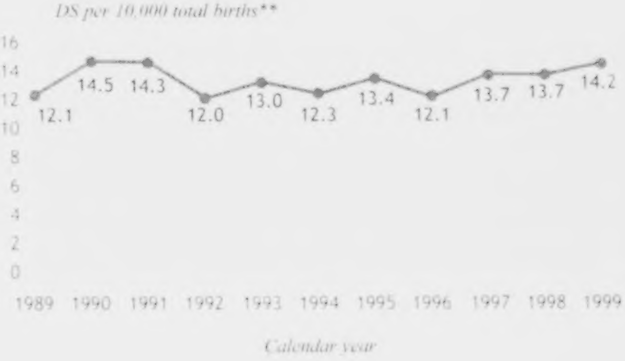
Provincial and Territorial Prevalence Rates

The prevalence rates for the combined three years 1997-1999 are shown in Figure 1.2 (see also Appendix D, Data Table D1.2). Although there appears to be considerable variation between the provinces and territories, the small number of cases and the large confidence intervals in the less populated provinces/territories (such as Prince Edward Island, Yukon and the Northwest Territories) must be taken into account when interpreting these rates. Variation in maternal age, as well as access to or utilization of prenatal diagnosis within a given province or territory, may explain some of the observed differences.

British Columbia, for example, has a high proportion of deliveries by women aged 35 years or older (18.1% of hospital deliveries) and a comparatively high birth prevalence of DS (16.9 per 10,000 total births), whereby the converse is observed in Newfoundland (10.1% of hospital deliveries by women aged 35 years or older and a birth prevalence of DS of 12.9 per 10,000 total births). The proportion of hospital deliveries by women aged 35 years or older within the provinces and territories is presented in Appendix D, Data Table D1.2. CCASS is unable to standardize birth prevalence rates by maternal age or to explore the issue of access and utilization of prenatal diagnosis among the provinces and territories and how this relates to the birth prevalence of DS.

Figure 1.1

Down syndrome (DS) rate,
Canada (excluding Nova Scotia), 1989-1999*



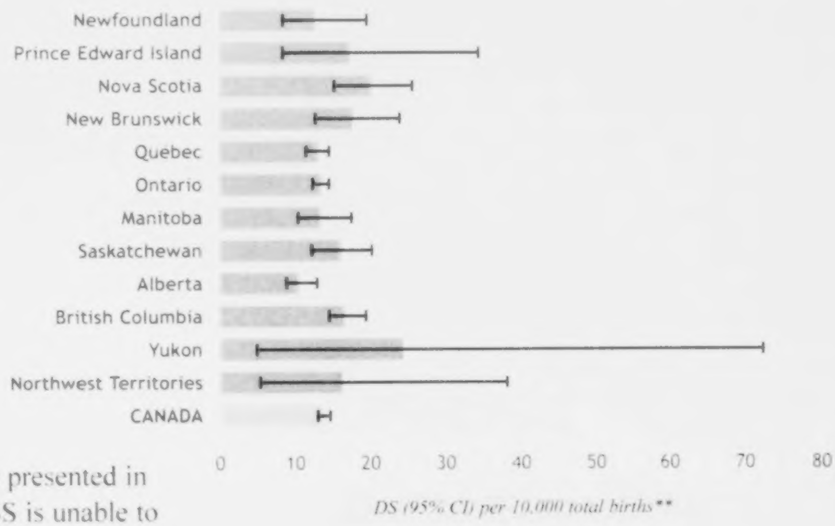
Source: Health Canada, Canadian Congenital Anomalies Surveillance System 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

Figure 1.2

Down syndrome (DS) rate, by province/territory,
*Canada, 1997-1999**



Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI = confidence interval.

International Comparisons

International comparisons of the 1999 rates of DS are presented in Table 1.3. Access to and utilization of prenatal screening, diagnostic testing and pregnancy termination services explain some of the observed variation. The impact of prenatal diagnosis where elective terminations are performed is evident. In 1999, 70.2% of DS pregnancies were terminated in Central East France, compared to 26.7% in Alberta, Canada.[17] The birth prevalence of DS is the highest in South America and the United Arab Emirates where legal terminations of pregnancy are not available.

Variation in the stillbirth definition may also contribute to international variations in the DS birth prevalence. England and Wales, for example, define a stillbirth according to a gestational age limit of 24 weeks or greater, whereas most Canadian provinces and territories define a stillbirth as a fetal death at a gestational age of 20 weeks or more, or a birth weight of 500 g or more. Consequently, pregnancies with DS that end in a spontaneous or induced abortion between 20 and 24 weeks would not be included in the birth prevalence in England and Wales, but most would be included in the Canadian DS birth prevalence.

Table 1.3

Down syndrome (DS) international rate,* by country/registry, *1999*

Country/registry	DS in live births and stillbirths	DS in live births, stillbirths and TOP
CANADA	14.4	N/A
Alberta, Canada	11.5	16.5
Atlanta, USA	12.0	N/A
Central East France	4.9	16.2
England and Wales	6.5	11.9
Finland	10.0	21.2
Hungary	8.1	9.3
Norway	13.7	16.0
South America	17.5	N/A
United Arab Emirates	18.0	N/A

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.[15]

*Per 10,000 total births.

TOP terminations of pregnancy.

N/A not available.

Impact of Prenatal Diagnosis on Birth Prevalence of Down Syndrome

The birth prevalence rates underestimate the true occurrence of DS, as early spontaneous abortions and terminations of pregnancy are not included. Estimates of spontaneous loss rates from mid-trimester to term are limited to studies of women of advanced maternal age and are highly variable, ranging from 15%-24%.[16] Prevalence rates that include terminations of pregnancy are captured among surveillance programs that maintain a fetal registry (Table 1.3). In Alberta, a fetal registry was established in 1997. In that year, there were 40 live births, 1 stillbirth and 15 terminations of pregnancy for the indication of DS. Two years later, in 1999, the Alberta registry recorded 42 live births, 3 stillbirths and 20 terminations of pregnancy.

Since 1993, the Prenatal Diagnosis Committee of the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) has been evaluating the use of prenatal diagnosis and the impact of elective termination on the birth prevalence rates of DS in jurisdictions where this option is available.[15] Over the past seven years, the Committee noted that the most significant decreases in the birth prevalence of DS occurred in countries or regions which had the highest rates of terminations.

Preventive Measures

All women are at some risk of having a child with DS. Women who delay childbearing until the later years of their reproductive life are at greater risk for having a child with DS, and there are no known measures for modifying or reducing this age-related risk. Prenatal testing is available to diagnose DS in pregnancy. As there is no "cure" for this condition, the only reproductive choices available are to either continue or terminate an affected pregnancy. From

International Comparisons

International comparisons of the 1999 rates of DS are presented in Table 1.3. Access to and utilization of prenatal screening, diagnostic testing and pregnancy termination services explain some of the observed variation. The impact of prenatal diagnosis where elective terminations are performed is evident. In 1999, 70.2% of DS pregnancies were terminated in Central East France, compared to 26.7% in Alberta, Canada.[15] The birth prevalence of DS is the highest in South America and the United Arab Emirates where legal terminations of pregnancy are not available.

Variation in the stillbirth definition may also contribute to international variations in the DS birth prevalence. England and Wales, for example, define a stillbirth according to a gestational age limit of 24 weeks or greater, whereas most Canadian provinces and territories define a stillbirth as a fetal death at a gestational age of 20 weeks or more, or a birth weight of 500 g or more. Consequently, pregnancies with DS that end in a spontaneous or induced abortion between 20 and 24 weeks would not be included in the birth prevalence in England and Wales, but most would be included in the Canadian DS birth prevalence.

Table 1.3

Down syndrome (DS) international rate,* by country/registry, *1999*

Country/registry	DS in live births and stillbirths	DS in live births, stillbirths and TOP
CANADA	**14.4**	**N/A**
Alberta, Canada	11.5	16.5
Atlanta, USA	12.0	N/A
Central East France	4.9	16.2
England and Wales	6.5	11.9
Finland	10.0	21.2
Hungary	8.1	9.3
Norway	13.7	16.0
South America	17.5	N/A
United Arab Emirates	18.0	N/A

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.[15]
*Per 10,000 total births.
TOP – terminations of pregnancy.
N/A – not available.

Impact of Prenatal Diagnosis on Birth Prevalence of Down Syndrome

The birth prevalence rates underestimate the true occurrence of DS, as early spontaneous abortions and terminations of pregnancy are not included. Estimates of spontaneous loss rates from mid-trimester to term are limited to studies of women of advanced maternal age and are highly variable, ranging from 15%-24%.[16] Prevalence rates that include terminations of pregnancy are captured among surveillance programs that maintain a fetal registry (Table 1.3). In Alberta, a fetal registry was established in 1997. In that year, there were 40 live births, 1 stillbirth and 15 terminations of pregnancy for the indication of DS. Two years later, in 1999, the Alberta registry recorded 42 live births, 3 stillbirths and 20 terminations of pregnancy.

Since 1993, the Prenatal Diagnosis Committee of the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) has been evaluating the use of prenatal diagnosis and the impact of elective termination on the birth prevalence rates of DS in jurisdictions where this option is available.[15] Over the past seven years, the Committee noted that the most significant decreases in the birth prevalence of DS occurred in countries or regions which had the highest rates of terminations.

Preventive Measures

All women are at some risk of having a child with DS. Women who delay childbearing until the later years of their reproductive life are at greater risk for having a child with DS, and there are no known measures for modifying or reducing this age-related risk. Prenatal testing is available to diagnose DS in pregnancy. As there is no "cure" for this condition, the only reproductive choices available are to either continue or terminate an affected pregnancy. From the perspective of tertiary prevention, children born with DS in Canada receive ongoing multidisciplinary attention to address their physical and intellectual needs, thus optimizing their overall health and well-being.

Summary

Down syndrome remains the most frequently occurring chromosomal abnormality in Canada. Since many women are delaying childbearing until their later reproductive years, and since prenatal testing is becoming increasingly available to pregnant women of all ages in Canada, ongoing analysis of DS rates is required to ensure accurate interpretation of the DS prevalence over time, as well as the impact that these two factors have on the Canadian DS rates.

References

1. Harper PS. *Practical Genetic Counselling*, 5th Edition. Boston: Butterworth Heinemann, 1998: 56-70.
2. Racial disparities in median age at death of persons with Down syndrome — United States, 1968-1997. *Morb Mortal Wkly Rep (MMWR)* 2001; 8: 463-5.
3. Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. *Lancet* 2002; 359: 1019-25.
4. Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Ann Neurol* 1985; 17: 278-82.
5. OMIM (Online Mendelian Inheritance of Man). *Down syndrome*. Entry #190685, 2001. (Available: www.3.ncbi.nlm.nih.gov).
6. Leonard S, Bower C, Petterson B, Leonard H. Survival of infants born with Down's syndrome: 1980-1996. *Paediatr Perinat Epidemiol* 2000; 2: 163-71.
7. Zipursky A, Peters M, Poon A. Megakaryoblastic leukemia and Down syndrome — A review. In: McCoy EE, Epstein CJ (Eds.), *Oncology and Immunology of Down syndrome*. New York: Alan R. Liss Publisher, 1987: 33-56.
8. Jones KL. *Smith's Recognizable Patterns of Human Malformation*, 4th Edition. Toronto: W.B. Saunders Company, 1988: 10-2.
9. Health Canada. *Canadian Perinatal Health Report, 2000*. Ottawa: Minister of Public Works and Government Services Canada, 2000.
10. Stoll C, Alembik Y, Dott B, Roth MP. Study of Down syndrome in 238,942 consecutive births. *Ann Genet* 1998; 41: 44-51.
11. Kallen B, Karlsson P, Lundell M, Wallgren A, Holm LE. Outcome of reproduction in women irradiated for hemangioma in infancy. *Radiat Res* 1998; 149: 202-8.
12. Kallen K. Down's syndrome and maternal smoking in early pregnancy. *Genet Epidemiol* 1997; 14: 77-84.
13. Kline J, Levin B, Kinney A, Stein Z, Susser M, Warburton D. Cigarette smoking and spontaneous abortion of known karyotype. Precise data but uncertain inferences. *Am J Epidemiol* 1995; 141: 417-27.
14. James SJ, Pogribna M, Pogribny IP, Melnyk S, Hine RJ, Gibson JB, Yi P, Tafoya DL, Swenson DH, Wilson VL, Gaylor DW. Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. *Am J Clin Nutr* 1999; 70: 495-501.
15. International Clearinghouse for Birth Defects Monitoring Systems. Chapter 11: Prenatal Diagnosis and Down Syndrome, 1999. In: *Annual Report*. Rome, Italy, 2001: 197-200.
16. Benn P, Egan JFX. Letters to the Editor: Survival of Down syndrome in utero. *Prenat Diagn* 2000: 20: 432-3.

2

Neural Tube Defects

Neural tube defects (NTDs) are congenital malformations of the central nervous system that are among the most common and serious of all congenital anomalies. Infant deaths attributed to NTDs have declined in Canada since the 1980s;[1] however, NTDs remain an important cause of mortality and morbidity in infancy, childhood and young adulthood.[2]

Neural tube defects result from the failure of the neural tube to close during early embryogenesis at approximately 25 to 27 days following conception.[3] Anencephaly and various forms of spina bifida are the most common NTDs. Failure of the caudal (upper) end of the neural tube to close results in anencephaly, a lethal defect characterized by the total or partial absence of the cranial vault and cerebral hemispheres.[3,4] Spina bifida is a defective closure of the neural tube in the vertebral column. Neurological problems associated with spina bifida depend on the size and location of the defect.[3,4] The clinical presentation ranges from no physical handicap to lifelong disabilities, including hydrocephalus, scoliosis, paralysis of the legs, bowel and bladder incontinence, seizures and mental handicap.[4]

Risk Factors

Neural tube defects occur in association with chromosome abnormalities, genetic syndromes and environmental teratogens. Most cases, however, have a multifactorial origin and occur in healthy couples with no specific pregnancy, health or genetic concerns.[5-8] The recurrence risk for couples with one child with an isolated NTD and no additional family history is 2%-5%, depending upon the baseline population risk.[5] It has been suggested that this figure may overestimate the current empirical risks of recurrence.[8]

Several epidemiological studies have demonstrated the protective effect of maternal periconceptional supplementation with multivitamins containing folic acid in the prevention of NTDs.[9-14] In particular, folic acid is believed to be protective against many of the multifactorially-inherited NTD cases.

Maternal factors associated with an increased risk for NTDs are low maternal vitamin B12 status, the use of anticonvulsant therapy, insulin-dependent diabetes mellitus and obesity. Low maternal vitamin B12 levels as a result of maternal disorders such as inflammatory bowel disease and pernicious anemia are considered independent risk factors for NTDs.[15]

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

Micromedia
ProQuest

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

The use of anticonvulsants, particularly valproic acid, in the first trimester of pregnancy increases a woman's risk of spina bifida in her offspring to 1%-2%.[16,17] The risk associated with insulin-dependent diabetes in women who are poorly controlled periconceptionally is approximately 1%.[18,19] Accumulating evidence suggests that obese women have approximately a two-fold increase in risk of an NTD-affected pregnancy.[18,20,21] It is not clear whether folic acid has the same protective effect in women with obesity or insulin-dependent diabetes, or in those receiving anticonvulsant therapy.[22]

> Folic acid, or folate, is a B vitamin essential for normal development of the brain and spinal cord, especially during the first four weeks of pregnancy. If taken before conception and in the first few weeks of pregnancy, folic acid works to reduce the risk of developing an NTD.[23]

Underlying genetic influences have not yet been fully identified. Research has implicated defects of homocysteine metabolism as a result of methylene tetrahydrofolate reductase (MTHFR) mutations as an independent genetic risk factor for NTDs.[24,25] The frequency of the C677T MTHFR variant in certain ethnic groups roughly correlates with the birth prevalence of NTDs.[24]

Researchers have studied the relationship between other genetic and environmental factors, such as twin pregnancies, hyperthermia, the use of ovulation-inducing drugs, exposure to chlorine disinfection by-products in drinking water and a short time interval between pregnancies, and NTDs. Consistent effects have not been demonstrated.[7,26,27] Variations in risk as a result of geographic location may be due, in part, to differences in case ascertainment and classification.[28,29]

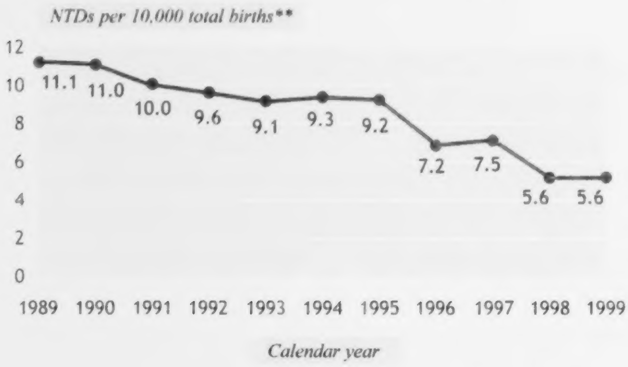
Prevalence Rate of Neural Tube Defects in Canada

In 1999, the birth prevalence of NTDs in Canada (all provinces and territories included) was 5.8 per 10,000 total births or 195 cases. The 1999 rate for Canada (excluding Nova Scotia) was 5.6 per 10,000 total births, a significant decline from the rate of 11.1 reported in 1989 (Figure 2.1; see also Appendix D, Data Tables D2.1-D2.3).

The birth prevalence of both anencephaly and spina bifida has decreased over the past decade. In 1999 in Canada (excluding Nova Scotia), the birth prevalence of anencephaly was 0.9 per 10,000 total births or 31 cases, down from 2.2 per 10,000 total births or 81 cases in 1989. Similarly, the birth prevalence of spina bifida in 1999 in Canada (excluding Nova Scotia) was 4.0 per 10,000 total births or 130 cases, down from 8.0 per 10,000 total

Figure 2.1

Neural tube defect (NTD) rate,
Canada (excluding Nova Scotia), 1989-1999*



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

births or 299 cases in 1989. Increased use of vitamin supplementation, as well as increased utilization of prenatal diagnosis and termination of affected pregnancies, all may have contributed to the reduction of NTD birth prevalence. The full impact of folic acid fortification (see "Preventive Measures" below) would likely not be apparent in the figures presented, as mandatory fortification did not begin until November 1998. Heightened surveillance is required to accurately assess the impact of folic acid fortification on the occurrence of NTDs in Canada.

Provincial and Territorial Prevalence Rates

There was considerable geographic variation in the birth prevalence of NTDs across Canada during the three-year period 1997-1999 (Figure 2.2; see also Appendix D, Data Tables D2.4-D2.6). The highest birth prevalence rates were in the Atlantic provinces of Newfoundland and Nova Scotia which had rates of 9.7 and 9.5 per 10,000 total births, respectively. Prince Edward Island, Yukon and the Northwest Territories did not report any NTD cases during this three-year period. Alberta's rate of 4.6 per 10,000 total births was the lowest reported birth prevalence in the country. Differences in dietary intake of folic acid and vitamin supplementation, and genetic makeup, as well as access to and utilization of prenatal testing services, all may have contributed to the observed variation.

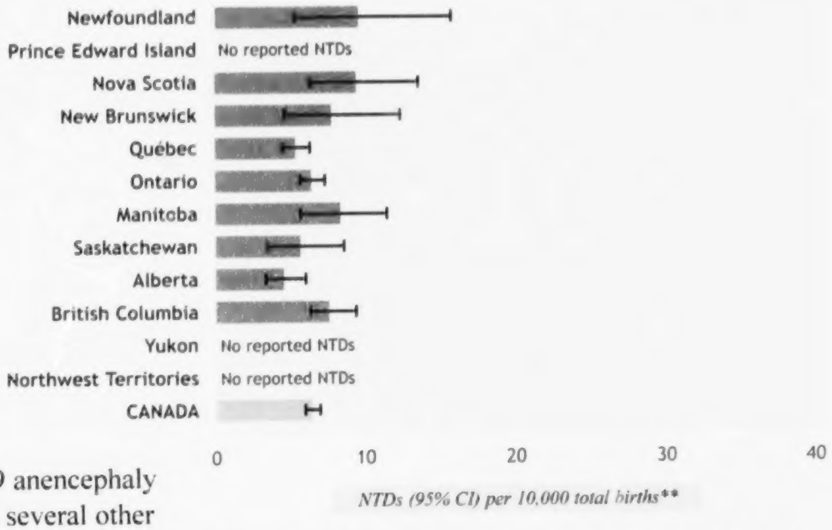
International Comparisons

International comparisons of the 1999 anencephaly and spina bifida rates for Canada and several other countries and jurisdictions are presented in Table 2.1. A number of countries, including Canada, experienced birth prevalence rates of anencephaly below 1.0 per 10,000 total births. Central East France's mid-trimester rate and birth prevalence of anencephaly were 1.5 and 0.0 per 10,000 total births, respectively, which suggests that 100% of anencephaly-affected pregnancies were prenatally detected and terminated. South America, where terminations of pregnancy are illegal, reported among the world's highest birth prevalence rates of anencephaly and spina bifida.

The Canadian birth prevalence of spina bifida was higher compared to rates reported from registries in Atlanta, France, England and Wales, Finland, and Hungary. However, the rates in the European countries increased substantially with the inclusion of pregnancy termination data. Unfortunately, Canada does not have good national estimates of rates of termination of pregnancies following prenatal diagnosis. England and Wales have a nation-wide maternal serum screening (MSS) program for NTDs. Their low NTD birth prevalence may reflect high utilization of the MSS program.

Figure 2.2

Neural tube defect (NTD) rate, by province/territory, *Canada, 1997-1999**



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI – confidence interval.

The use of anticonvulsants, particularly valproic acid, in the first trimester of pregnancy increases a woman's risk of spina bifida in her offspring to 1%-2%.[16,17] The risk associated with insulin-dependent diabetes in women who are poorly controlled periconceptionally is approximately 1%.[18,19] Accumulating evidence suggests that obese women have approximately a two-fold increase in risk of an NTD-affected pregnancy.[18,20,21] It is not clear whether folic acid has the same protective effect in women with obesity or insulin-dependent diabetes, or in those receiving anticonvulsant therapy.[22]

[illegible]

Underlying genetic influences have not yet been fully identified. Research has implicated defects of homocysteine metabolism as a result of methylene tetrahydrofolate reductase (MTHFR) mutations as an independent genetic risk factor for NTDs.[24,25] The frequency of the C677T MTHFR variant in certain ethnic groups roughly correlates with the birth prevalence of NTDs.[24]

Researchers have studied the relationship between other genetic and environmental factors, such as twin pregnancies, hyperthermia, the use of ovulation-inducing drugs, exposure to chlorine disinfection by-products in drinking water and a short time interval between pregnancies, and NTDs. Consistent effects have not been demonstrated.[7,26,27] Variations in risk as a result of geographic location may be due, in part, to differences in case ascertainment and classification.[28,29]

Prevalence Rate of Neural Tube Defects in Canada

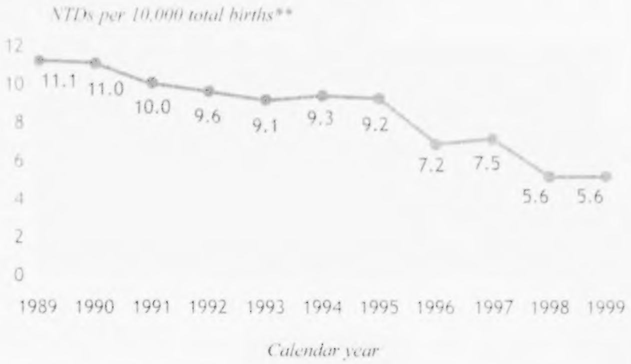
In 1999, the birth prevalence of NTDs in Canada (all provinces and territories included) was 5.8 per 10,000 total births or 195 cases. The 1999 rate for Canada (excluding Nova Scotia) was 5.6 per 10,000 total births, a significant decline from the rate of 11.1 reported in 1989 (Figure 2.1; see also Appendix D, Data Tables D2.1-D2.3).

The birth prevalence of both anencephaly and spina bifida has decreased over the past decade. In 1999 in Canada (excluding Nova Scotia), the birth prevalence of anencephaly was 0.9 per 10,000 total births or 31 cases, down from 2.2 per 10,000 total births or 81 cases in 1989. Similarly, the birth prevalence of spina bifida in 1999 in Canada (excluding Nova Scotia) was 4.0 per 10,000 total births or 130 cases, down from 8.0 per 10,000 total

Figure 2.1

Neural tube defect (NTD) rate,

Canada (excluding Nova Scotia), 1989-1999*



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

births or 299 cases in 1989. Increased use of vitamin supplementation, as well as increased utilization of prenatal diagnosis and termination of affected pregnancies, all may have contributed to the reduction of NTD birth prevalence. The full impact of folic acid fortification (see "Preventive Measures" below) would likely not be apparent in the figures presented, as mandatory fortification did not begin until November 1998. Heightened surveillance is required to accurately assess the impact of folic acid fortification on the occurrence of NTDs in Canada.

Provincial and Territorial Prevalence Rates

There was considerable geographic variation in the birth prevalence of NTDs across Canada during the three-year period 1997-1999 (Figure 2.2; see also Appendix D, Data Tables D2.4-D2.6). The highest birth prevalence rates were in the Atlantic provinces of Newfoundland and Nova Scotia which had rates of 9.7 and 9.5 per 10,000 total births, respectively. Prince Edward Island, Yukon and the Northwest Territories did not report any NTD cases during this three-year period. Alberta's rate of 4.6 per 10,000 total births was the lowest reported birth prevalence in the country. Differences in dietary intake of folic acid and vitamin supplementation, and genetic makeup, as well as access to and utilization of prenatal testing services, all may have contributed to the observed variation.

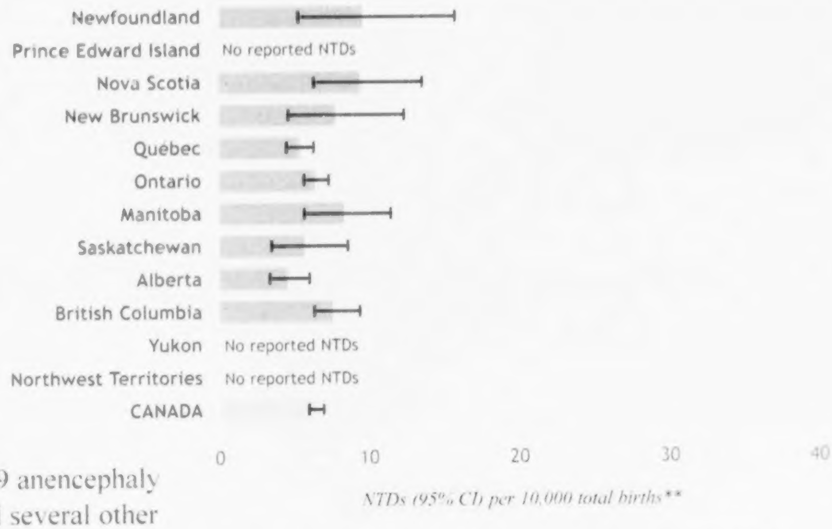
International Comparisons

International comparisons of the 1999 anencephaly and spina bifida rates for Canada and several other countries and jurisdictions are presented in Table 2.1. A number of countries, including Canada, experienced birth prevalence rates of anencephaly below 1.0 per 10,000 total births. Central East France's mid-trimester rate and birth prevalence of anencephaly were 1.5 and 0.0 per 10,000 total births, respectively, which suggests that 100% of anencephaly-affected pregnancies were prenatally detected and terminated. South America, where terminations of pregnancy are illegal, reported among the world's highest birth prevalence rates of anencephaly and spina bifida.

The Canadian birth prevalence of spina bifida was higher compared to rates reported from registries in Atlanta, France, England and Wales, Finland, and Hungary. However, the rates in the European countries increased substantially with the inclusion of pregnancy termination data. Unfortunately, Canada does not have good national estimates of rates of termination of pregnancies following prenatal diagnosis. England and Wales have a nation-wide maternal serum screening (MSS) program for NTDs. Their low NTD birth prevalence may reflect high utilization of the MSS program.

Figure 2.2

Neural tube defect (NTD) rate, by province/territory, *Canada, 1997-1999**



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI — confidence interval.

Table 2.1

Anencephaly and spina bifida international rates,* by country/registry, *1999*

Country/registry	Anencephaly		Spina bifida	
	Live births and stillbirths	Live births, stillbirths and TOP	Live births and stillbirths	Live births, stillbirths and TOP
CANADA	0.9	N/A	4.0	N/A
Alberta, Canada	1.0	1.3	3.4	3.9
Atlanta, USA	1.5	N/A	0.6	N/A
Central East France	0.0	1.5	0.7	3.5
England and Wales	0.4	2.7	1.0	2.8
Finland	0.2	3.1	2.2	3.4
Hungary	0.1	2.1	1.6	3.1
Norway	2.5	5.3	4.2	6.2
South America	7.6	N/A	11.7	N/A
United Arab Emirates	7.7	N/A	6.4	N/A

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.[30]

*Per 10,000 total births.

TOP = terminations of pregnancy.

N/A = not available.

Impact of Prenatal Diagnosis on Birth Prevalence of Neural Tube Defects

Prenatal testing utilizing MSS and second trimester ultrasound is highly accurate for NTD screening in low-risk populations.[31] The sensitivity of second trimester ultrasound in the detection of isolated cases of spina bifida ranges from 50%-100%, depending on the operator's experience, the sophistication of the technology used, fetal positioning and the maternal habitus.[32] The sensitivity of second trimester ultrasound in the detection of anencephaly is consistently in the range of 98%.[33] Prenatal magnetic resonance imaging can be helpful in further delineating fetal central nervous system anomalies and may increasingly be used to follow up abnormal ultrasound results.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends that all pregnant women be offered the option of an 18 to 19 week ultrasound examination.[34,35] In addition, the SOGC states that all women should be provided with the choice of MSS for Down syndrome (DS), trisomy 18 and open NTDs in the second trimester of pregnancy.[36]

Table 2.1 illustrates the potential impact of prenatal testing on the birth prevalence of NTDs, with markedly higher overall rates in jurisdictions that counted terminated pregnancies. Fetal registry data from the Alberta Congenital Anomalies Surveillance System (ACASS) support the contention that prenatal testing has an impact on the NTD birth prevalence in Canada.[37]

Preventive Measures

National medical specialty societies, such as the Canadian Paediatric Society,[38] the SOGC and the Canadian College of Medical Geneticists,[39] recommend daily periconceptional folic acid supplementation for women who could become pregnant to reduce their risk of having an NTD-affected pregnancy. However, a survey conducted of women of childbearing age in Canada revealed

Table 2.1

Anencephaly and spina bifida international rates,* by country/registry, *1999*

Country/registry	Anencephaly		Spina bifida	
	Live births and stillbirths	Live births, stillbirths and TOP	Live births and stillbirths	Live births, stillbirths and TOP
CANADA	**0.9**	**N/A**	**4.0**	**N/A**
Alberta, Canada	1.0	1.3	3.4	3.9
Atlanta, USA	1.5	N/A	0.6	N/A
Central East France	0.0	1.5	0.7	3.5
England and Wales	0.4	2.7	1.0	2.8
Finland	0.2	3.1	2.2	3.4
Hungary	0.1	2.1	1.6	3.1
Norway	2.5	5.3	4.2	6.2
South America	7.6	N/A	11.7	N/A
United Arab Emirates	7.7	N/A	6.4	N/A

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.[30]
*Per 10,000 total births.
TOP – terminations of pregnancy.
N/A – not available.

Impact of Prenatal Diagnosis on Birth Prevalence of Neural Tube Defects

Prenatal testing utilizing MSS and second trimester ultrasound is highly accurate for NTD screening in low-risk populations.[31] The sensitivity of second trimester ultrasound in the detection of isolated cases of spina bifida ranges from 50%-100%, depending on the operator's experience, the sophistication of the technology used, fetal positioning and the maternal habitus.[32] The sensitivity of second trimester ultrasound in the detection of anencephaly is consistently in the range of 98%.[33] Prenatal magnetic resonance imaging can be helpful in further delineating fetal central nervous system anomalies and may increasingly be used to follow up abnormal ultrasound results.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends that all pregnant women be offered the option of an 18 to 19 week ultrasound examination.[34,35] In addition, the SOGC states that all women should be provided with the choice of MSS for Down syndrome (DS), trisomy 18 and open NTDs in the second trimester of pregnancy.[36]

Table 2.1 illustrates the potential impact of prenatal testing on the birth prevalence of NTDs, with markedly higher overall rates in jurisdictions that counted terminated pregnancies. Fetal registry data from the Alberta Congenital Anomalies Surveillance System (ACASS) support the contention that prenatal testing has an impact on the NTD birth prevalence in Canada.[37]

Preventive Measures

National medical specialty societies, such as the Canadian Paediatric Society,[38] the SOGC and the Canadian College of Medical Geneticists,[39] recommend daily periconceptional folic acid supplementation for women who could become pregnant to reduce their risk of having an NTD-affected pregnancy. However, a survey conducted of women of childbearing age in Canada revealed limited awareness of the benefits of folic acid.[40] Health Canada has recently launched a national campaign to increase awareness of folic acid and its potential benefits.[2,27]

In light of the challenges of effectively promoting widespread supplementation, food fortification with folic acid became mandatory in Canada in November 1998. The full impact of this population-wide intervention must still be determined.

The role of prenatal diagnosis and pregnancy termination as a secondary preventive measure has already been reviewed. An additional preventive measure to reduce the morbidity and mortality due to NTDs is fetal surgery. Preliminary reports of the benefits of intrauterine surgical spina bifida repair on neonatal and infant morbidity have been encouraging, but experience remains very limited.[41] Clearly, primary preventive efforts aimed at increasing periconceptional folic acid consumption remain the optimal approach.

Summary

The birth prevalence of NTDs has declined over the past decade in Canada. Several factors may be responsible for the observed decline, including increased utilization of prenatal diagnosis and increased folic acid consumption. Ongoing surveillance, including the ascertainment of prenatally diagnosed cases, will be required to accurately determine the causes of the observed trends and inter-provincial/territorial variations.

References

1. Wen SW, Liu S, Joseph KS, Rouleau J, Allen A. Patterns of infant mortality caused by major congenital anomalies. *Teratology* 2000; 61: 342-6.
2. Van Allen MI, McCourt C, Lee NS. *Preconception health: folic acid for the primary prevention of neural tube defects. A resource document for health professionals, 2002*. Ottawa: Minister of Public Works and Government Services, Canada, 2002.
3. Moore KL, Persaud TVN. *The Developing Human. Clinically Oriented Embryology*, 6th Edition. Toronto: W.B. Saunders Company, 1998: chapter 18.
4. Tolmie J. Neural tube defects and other congenital malformations of the central nervous system. In: Emery A, Rimon D (Eds.), *Principles and Practice of Medical Genetics*, 3rd Edition. New York: Churchill Livingston, 1997: 2145-76.
5. Hall JG, Solehdin F. Genetics of neural tube defects. *Men Retard Dev Disabil* 1999; 4: 269-81.
6. Hall JG, Friedman JM, Kenna BA, Popkin J, Jawanda M, Arnold W. Clinical, genetic and epidemiological factors in neural tube defects. *Am J Hum Genet* 1988; 43: 827-37.
7. Myrianthopoulos NC, Melnick M. Studies in neural tube defects. I. Epidemiologic and etiologic aspects. *Am J Med Genet* 1987; 4: 738-96.
8. Harper PS. *Practical Genetic Counselling*, 5th Edition. Boston: Butterworth Heinmann, 1998: 175-6.
9. Milunsky A, Jick H, Jick SS et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. *JAMA* 1989; 262: 2847-52.
10. Wald N, Sneddon J, Densem J, Frost C, Stone R. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991; 338: 131-7.
11. Czeizel AE, Dudas E. Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992; 327: 1832-5.
12. Mulinare J, Cordero JF, Erickson JD, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. *JAMA* 1988; 206: 3141-5.
13. Bower C, Stanley FJ. Dietary folate as a risk factor for neural tube defects: evidence from a case-control study in Western Australia. *Med J Aust* 1989; 150: 613-9.

14. Werler MM, Shapiro S, Mitchell AA. Periconceptional folic acid exposure and risk of occurrence of neural tube defects. *JAMA* 1993; 269: 1257-61.

15. Kirke PN, Daly LE, Molloy A, Weir DG, Scott JM. Letter to Editor: Maternal folate status and risk of neural tube defects. *Lancet* 1996; 348: 67-8.

16. Robert E, Guibaud P. Maternal valproic acid and congenital neural tube defects. *Lancet* 1982; 2: 937.

17. Guibaud S, Robert E, Simplot A et al. Prenatal diagnosis of spina bifida after first-trimester valproate exposure. *Prenat Diagn* 1993; 13: 772.

18. Moore LL, Singer MR, Bradlee ML, Rothman KJ, Milunsky A. A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. *Epidemiology* 2000; 11: 689-94.

19. Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics* 1990; 85: 1-9.

20. Waller DK, Mills JL, Simpson JL et al. Are obese women at higher risk for producing malformed offspring? *Am J Obstet Gynecol* 1994; 170: 541.

21. Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect: Affected pregnancies among obese women. *JAMA* 1996; 275: 1093.

22. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol* 2001; 153: 961-8.

23. Reproductive Health Section, Health Canada. *National Folic Acid Campaign*. 2002. (Available: www.hc-sc.gc.ca/pphb-dgspsp/rhs-ssg/index.html).

24. Botto LD, Mulinare J. Methylenetetrahydrofolate reductase gene and neural tube defects. *Am J Epidemiol* 1999; 150: 323-42.

25. Van der Put NMJ, Eskes TKAB et al. Is the common 677-T mutation in the methylenetetrahydrofolate reductase gene a risk factor for neural tube defects? A meta-analysis. *Q J Med* 1997; 90: 111.

26. Dodds L, King WD. Relation between trihalomethane compounds and birth defects. *Occ Environ Med* 2001; 7: 443-6.

27. Kallen B, Cocchi G, Knudsen LB et al. International study of sex ratio and twinning of neural tube defects. *Teratology* 1994; 50: 322-31.

28. Elwood JM, Elwood JH. *Epidemiology of anencephalus and spina bifida*. Oxford: Oxford University Press, 1980.

29. Borman B, Cryer C. Fallacies of international and national comparisons of disease occurrence in the epidemiology of neural tube defects. *Teratology* 1990; 42: 405-12.

30. International Clearinghouse for Birth Defects Monitoring Systems. *Annual Report*. Rome, Italy, 2001.

31. Milunsky A. Maternal serum screening for neural tube and other defects. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 635-44.

32. Bianchi DW, Crombleholme TM, D'Alton ME. Prenatal Imaging. In: *Fetology: Diagnosis and Management of the fetal patient*. Toronto: McGraw-Hill Medical Publishing Division, 2000: 6-9.

33. Boyd PA, Wellesley DG, De Walle HEK et al. Evaluation of the prenatal diagnosis of neural tube defects by fetal ultrasonographic examination in different centres across Europe. *J Med Screen* 2000; 7: 169-74.

34. Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Guidelines for ultrasound as part of routine prenatal care. *SOGC Journal* 1999; August: 78. (Available: http://sogc.medical.org/SOGCnet/sogc_docs/common/guide/pdfs/ps78.pdf).

35. Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Genetic indications for prenatal diagnosis. *SOGC Journal* 2001; June: 105.

36. Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Prenatal genetic screening for Down syndrome and open neural tube defects using maternal serum marker screening. *SOGC Journal* 1999; August: 79.

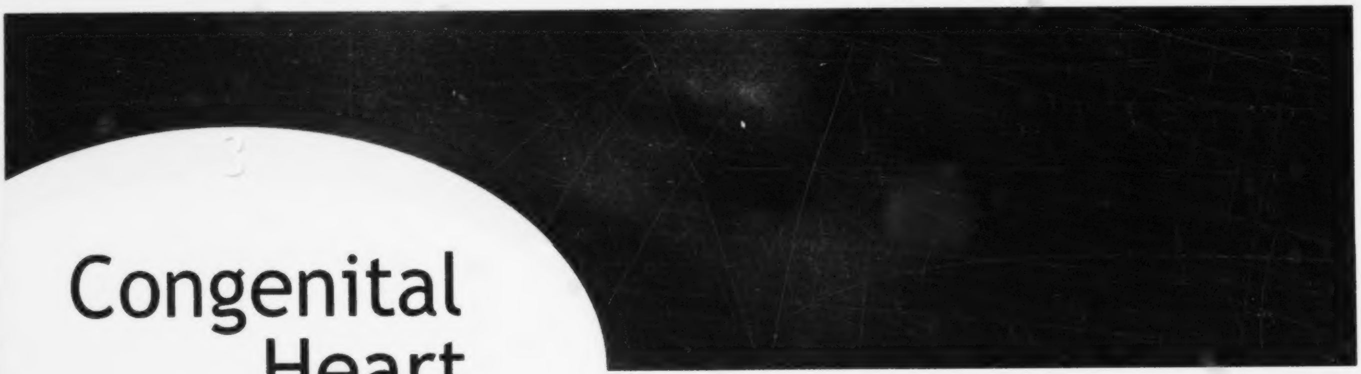
37. Lowry RB, Sibbald BS, Wang FL. *Alberta Congenital Anomalies Surveillance System Report. Fourth report: 1980-1998.* Alberta Children's Hospital Research Centre, Alberta Health, Health Surveillance and the Division of Vital Statistics, Alberta Registries, 2001.

38. Drug Therapy and Hazardous Substances Committee, Canadian Paediatric Society. Periconceptional use of folic acid for reduction of the risk of neural tube defects. *Paediatrics and Child Health* 1997; 2: 152-4.

39. Society of Obstetricians and Gynaecologists of Canada. SOGC Policy Statement. Recommendations on the use of folic acid for the prevention of neural tube defects. *SOGC Journal* 1993; March Supplement: 41-6.

40. Bonin MM, Bretzlaff JA, Therrien MA, Trowe BH. Knowledge of periconceptional folic acid for the prevention of neural tube defects. *Arch Fam Med* 1998; 7: 438-42.

41. Bianchi DW, Crombleholme TM, D'Alton ME. Myelomeningocele. In: *Fetology. Diagnosis and Management of the fetal patient.* Toronto: McGraw-Hill Medical Publishing Division, 2000: 159-71.



Congenital Heart Defects

Congenital heart defects (CHDs) are among the most common structural anomalies, diagnosed in approximately 1 in 100–150 newborns. Most children with CHDs are born to couples with no prior family history or maternal risk factors.

Advances in diagnosis and surgical treatments have led to earlier diagnosis and a dramatic reduction in childhood mortality and morbidity.[1] However, serious heart defects continue to have an impact on the health of affected children. Congenital heart anomalies are the leading cause of deaths attributable to congenital anomalies in Canada.[2] The infant mortality rate directly due to CHDs in Canada for the combined three years 1996–1998 was 4.7 per 10,000 live births. Minor and more common defects such as ventricular and atrial septal defects carry a good prognosis. However, complex heart anomalies are associated with significant morbidity and mortality.[3] Hypoplastic left heart syndrome (HLHS), for example, is a relatively rare anomaly which is responsible for 25% of all cardiac deaths in the first year of life.[4] Between 1981 and 1998, 894 infants were born with HLHS in Canada. Until the 1980s, HLHS was uniformly fatal. As a result of the advances in staged surgical treatment and perioperative and postoperative neonatal management, a small number of affected children are now surviving. The long-term neurodevelopmental outcome and quality of life for children receiving such treatment is largely unknown.[5-7]

Hypoplastic Left Heart Syndrome (HLHS)

This critical heart defect is characterized by an underdeveloped left ventricle in combination with stenosis or atresia (absence) of the mitral or aortic valves. Following birth, upon closure of the ductus arteriosus, the baby goes into cardiovascular failure as the right ventricle is cut off from its outlet to the aorta. In the past, HLHS was uniformly fatal.

The introduction of the Norwood three-step reconstructive operation and heart transplantation in neonates has improved the prognosis of infants with this complex heart lesion.

Conotruncal Heart Defects

Approximately 25% of all heart defects are conotruncal anomalies. Conotruncal heart defects are major abnormalities of the heart's chambers or blood vessels leading to and from the heart. One third to one half of affected infants die before their first birthday. Included in the category of conotruncal heart defects are tetralogy of Fallot, transposition of the great vessels, single ventricle and truncus arteriosus. Conotruncal heart malformations may be components of specific syndromes, e.g., velo-cardiofacial syndrome. Approximately 30% of isolated cases of conotruncal anomalies will carry a chromosome 22q11.2 microdeletion.[8]

Risk Factors

The majority of isolated CHDs are multifactorially inherited. They are also frequently identified in combination with other congenital malformations, chromosome abnormalities, as part of a genetic syndrome, or are directly a result of a teratogen exposure.

Congenital heart defects are a prominent clinical finding in chromosome aneuploidies, including Down syndrome (DS), trisomies 13 and 18, and Turner syndrome (45X). Furthermore, specific CHDs occur more frequently with particular chromosomal abnormalities. For example, atrioventricular canal defects and coarctation of the aorta are comparatively more frequent than any other CHDs in individuals with DS and Turner syndrome, respectively.[9] The discovery of chromosome 22q11 microdeletion, commonly seen in cases with non-syndromic conotruncal heart anomalies, has provided further insight into understanding the underlying genetic causes of CHDs.

A large body of evidence has established the link between periconceptional supplementation with folic acid and reduction in occurrence and recurrence of neural tube defects (NTDs). Emerging studies are now suggesting a similar protective effect with multivitamins containing folic acid against the complex conotruncal heart defects.[10-12]

Approximately 2% of CHDs are believed to be due to environmental agents.[13] Known teratogens are maternal alcohol abuse, rubella, hydantoin, thalidomide and accutane. Poorly controlled insulin-dependent diabetes and phenylketonuria are known maternal risk factors for CHDs. Although not uniformly supported, the following have been reported as independent risk factors for CHDs: high retinol intake from supplements;[14] maternal exposures to herbicides;[15] febrile illness;[16] monozygote twinning;[9] advanced maternal age greater than 40 years;[9] and paternal age greater than 35 years.[17] The prevalence rate of CHDs based on maternal age is presented in Table 3.1.

Table 3.1

Congenital heart defect (CHD) rate,* by maternal age, *California, 1995*

Maternal age (years)	CHD rate
< 18	37.0
18-19	40.0
20-24	34.0
25-29	35.0
30-34	47.0
> 35	84.0

Source: California Birth Defects Monitoring Program, 1995.[18]
*Per 10,000 total births.

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

Micromedia
ProQuest

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

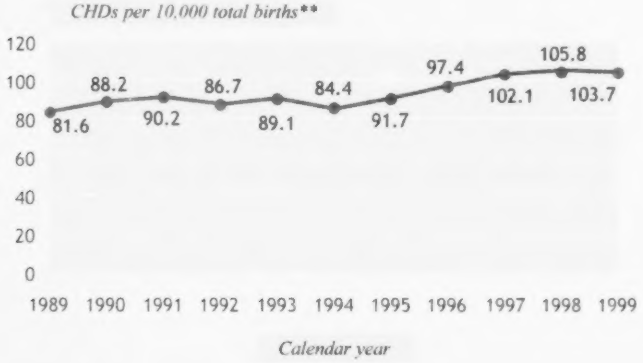
Prevalence Rate of Congenital Heart Defects in Canada

Determining the true birth prevalence of CHDs is hindered by challenges in data collection and the verification of diagnosis. Under-ascertainment of minor CHDs in the initial newborn period is likely, particularly in the absence of echocardiography. Over-ascertainment of certain CHDs also occurs.[1,19] For example, a patent ductus arteriosus reported in a preterm infant is not necessarily a congenital anomaly as the ductus is physiologically present in all fetuses prior to 34 weeks in pregnancy. In view of these limitations, a general overview of CHDs will be presented, followed by a closer review of HLHS which is more likely to be accurately diagnosed in early infancy.

In Canada in 1999 (all provinces and territories included), the birth prevalence of CHDs was 104.0 per 10,000 total births or 3,518 affected cases. The reported birth prevalence of CHDs for Canada (excluding Nova Scotia) has increased over the 10-year interval from 1989-1999 (Figure 3.1; see also Appendix D, Data Table D3.1). Ventricular and atrial septal defects are the most common CHDs, and there has been an increasing trend in the birth prevalence of these two septal defects.

Figure 3.1

Congenital heart defect (CHD) rate, *Canada (excluding Nova Scotia),* 1989-1999*



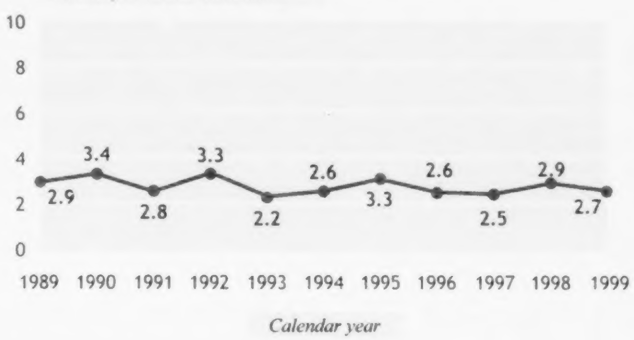
Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

Figure 3.2

Hypoplastic left heart syndrome (HLHS) rate, *Canada (excluding Nova Scotia),* 1989-1999*



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

In 1999, for example, the prevalence rates for Canada (excluding Nova Scotia) for these two defects were 35.6 and 42.3 per 10,000 total births, up from the 1989 rates of 32.8 and 22.3 per 10,000 total births, respectively. Coding of septal defects can be highly inconsistent. Small ventricular septal defects, for example, are often benign and resolve spontaneously in early infancy. Some jurisdictions/registries include such non-clinically significant septal defects in their counts of CHDs, while others do not.

The increasing trend in the overall CHD birth prevalence may be reflective of a change in ascertainment over time, or an increase in birth rate among older women. Unfortunately, it is not possible to stratify the national CHD data by maternal age, associated chromosome anomalies or other risk factors. An increasing trend in the CHD rate has also been noted in many other countries, largely attributable to increased ascertainment.[20]

In Canada in 1999 (all provinces and territories included), the birth prevalence of HLHS was 2.8 per 10,000 total births, or 94 cases. The rate for Canada (excluding Nova Scotia) has remained relatively constant over the 10-year period from 1989-1999 (Figure 3.2; see also Appendix D, Data Table D3.2).

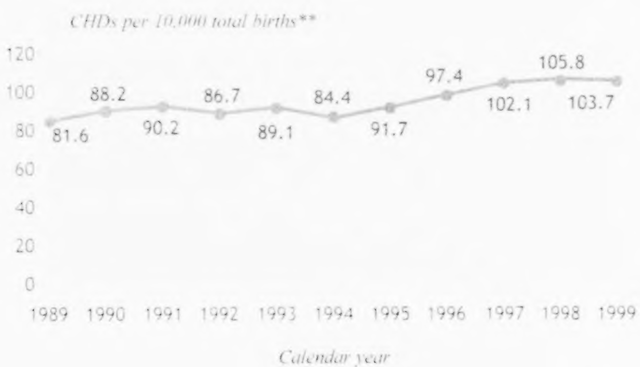
Prevalence Rate of Congenital Heart Defects in Canada

Determining the true birth prevalence of CHDs is hindered by challenges in data collection and the verification of diagnosis. Under-ascertainment of minor CHDs in the initial newborn period is likely, particularly in the absence of echocardiography. Over-ascertainment of certain CHDs also occurs.[1,19] For example, a patent ductus arteriosus reported in a preterm infant is not necessarily a congenital anomaly as the ductus is physiologically present in all fetuses prior to 34 weeks in pregnancy. In view of these limitations, a general overview of CHDs will be presented, followed by a closer review of HLHS which is more likely to be accurately diagnosed in early infancy.

In Canada in 1999 (all provinces and territories included), the birth prevalence of CHDs was 104.0 per 10,000 total births or 3,518 affected cases. The reported birth prevalence of CHDs for Canada (excluding Nova Scotia) has increased over the 10-year interval from 1989-1999 (Figure 3.1; see also Appendix D, Data Table D3.1). Ventricular and atrial septal defects are the most common CHDs, and there has been an increasing trend in the birth prevalence of these two septal defects.

Figure 3.1

Congenital heart defect (CHD) rate, *Canada (excluding Nova Scotia),* 1989-1999*



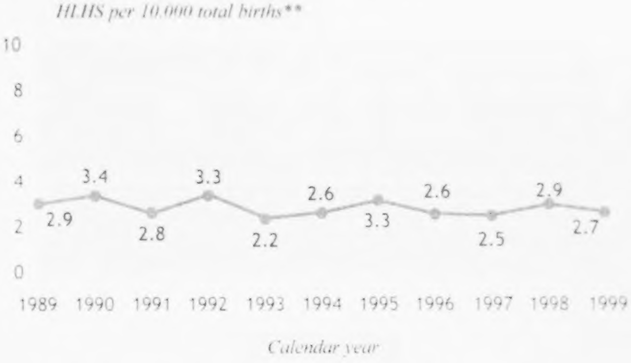
Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

Figure 3.2

Hypoplastic left heart syndrome (HLHS) rate, *Canada (excluding Nova Scotia),* 1989-1999*



Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

In 1999, for example, the prevalence rates for Canada (excluding Nova Scotia) for these two defects were 35.6 and 42.3 per 10,000 total births, up from the 1989 rates of 32.8 and 22.3 per 10,000 total births, respectively. Coding of septal defects can be highly inconsistent. Small ventricular septal defects, for example, are often benign and resolve spontaneously in early infancy. Some jurisdictions/registries include such non-clinically significant septal defects in their counts of CHDs, while others do not.

The increasing trend in the overall CHD birth prevalence may be reflective of a change in ascertainment over time, or an increase in birth rate among older women. Unfortunately, it is not possible to stratify the national CHD data by maternal age, associated chromosome anomalies or other risk factors. An increasing trend in the CHD rate has also been noted in many other countries, largely attributable to increased ascertainment.[20]

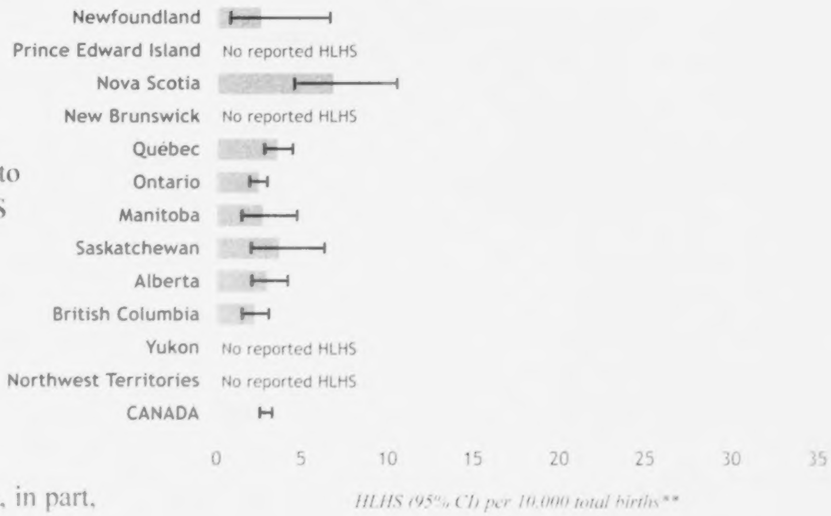
In Canada in 1999 (all provinces and territories included), the birth prevalence of HLHS was 2.8 per 10,000 total births, or 94 cases. The rate for Canada (excluding Nova Scotia) has remained relatively constant over the 10-year period from 1989-1999 (Figure 3.2; see also Appendix D, Data Table D3.2).

Provincial and Territorial Prevalence Rates

The validity of CCASS-reported rates of HLHS has been demonstrated to be superior to many other CHD categories.[21] The provincial and territorial comparisons shown in Figure 3.3 (see also Appendix D, Data Table D3.3) are therefore limited to HLHS. The birth prevalence of HLHS for the combined three years 1997-1999 ranges from 0 per 10,000 total births in Prince Edward Island, New Brunswick, Yukon and the Northwest Territories to 6.8 per 10,000 total births (20 cases) in Nova Scotia. Variations in the provincial/territorial rates may be due, in part, to differences in case ascertainment and in the proportion of births to older women.

Figure 3.3

Hypoplastic left heart syndrome (HLHS) rate, by province/territory, *Canada, 1997-1999**



Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI – confidence interval.

International Comparisons

The International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) limits the reporting of CHDs to three complex anomalies. These specific anomalies, HLHS, tetralogy of Fallot and transposition of the great vessels, are readily diagnosed early in life or at autopsy. The rates of HLHS are presented in Table 3.2. As noted, there are considerable differences in the reported rates of HLHS, varying from 0.5 per 10,000 in England and Wales to 5.1 per 10,000 total births in the United Arab Emirates.

Table 3.2

Hypoplastic left heart syndrome (HLHS) international rate,* by country/registry, *1999*

Country/registry	HLHS in live births and stillbirths	HLHS in live births, stillbirths and TOP
CANADA	2.8	N/A
Alberta, Canada	2.1	2.1
Atlanta, USA	2.9	N/A
Australia (1998)	1.5	1.9
Central East France	1.5	2.3
England and Wales	0.5	0.8
Finland	4.0	4.5
Hungary	0.8	0.8
Norway	2.5	3.3
South America	1.1	N/A
United Arab Emirates	5.1	N/A

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.[40]

*Per 10,000 total births.

TOP – terminations of pregnancy.

N/A – not available.

Impact of Prenatal Diagnosis on Birth Prevalence of Congenital Heart Defects

Fetal echocardiography, performed at 20 to 23 weeks in pregnancy, is increasingly used to identify complex CHDs. This allows parental choice regarding the management and outcome of an affected pregnancy. Couples electing to continue their pregnancy can plan for altered obstetric and neonatal management, including delivery at a

Provincial and Territorial Prevalence Rates

The validity of CCASS-reported rates of HLHS has been demonstrated to be superior to many other CHD categories.[21] The provincial and territorial comparisons shown in Figure 3.3 (see also Appendix D, Data Table D3.3) are therefore limited to HLHS. The birth prevalence of HLHS for the combined three years 1997-1999 ranges from 0 per 10,000 total births in Prince Edward Island, New Brunswick, Yukon and the Northwest Territories to 6.8 per 10,000 total births (20 cases) in Nova Scotia. Variations in the provincial/territorial rates may be due, in part, to differences in case ascertainment and in the proportion of births to older women.

International Comparisons

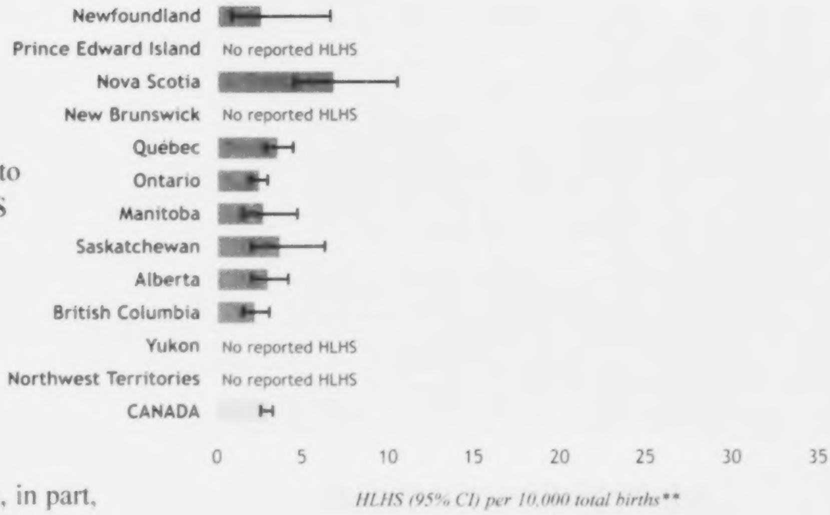
The International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) limits the reporting of CHDs to three complex anomalies. These specific anomalies, HLHS, tetralogy of Fallot and transposition of the great vessels, are readily diagnosed early in life or at autopsy. The rates of HLHS are presented in Table 3.2. As noted, there are considerable differences in the reported rates of HLHS, varying from 0.5 per 10,000 in England and Wales to 5.1 per 10,000 total births in the United Arab Emirates.

Impact of Prenatal Diagnosis on Birth Prevalence of Congenital Heart Defects

Fetal echocardiography, performed at 20 to 23 weeks in pregnancy, is increasingly used to identify complex CHDs. This allows parental choice regarding the management and outcome of an affected pregnancy. Couples electing to continue their pregnancy can plan for altered obstetric and neonatal management, including delivery at a

Figure 3.3

Hypoplastic left heart syndrome (HLHS) rate, by province/territory, *Canada, 1997-1999**



Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI – confidence interval.

Table 3.2

Hypoplastic left heart syndrome (HLHS) international rate,* by country/registry, *1999*

Country/registry	HLHS in live births and stillbirths	HLHS in live births, stillbirths and TOP
CANADA	2.8	N/A
Alberta, Canada	2.1	2.1
Atlanta, USA	2.9	N/A
Australia (1998)	1.5	1.9
Central East France	1.5	2.3
England and Wales	0.5	0.8
Finland	4.0	4.5
Hungary	0.8	0.8
Norway	2.5	3.3
South America	1.1	N/A
United Arab Emirates	5.1	N/A

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.[20]

*Per 10,000 total births.

TOP – terminations of pregnancy.

N/A – not available.

tertiary care centre and prompt intensive neonatal care, which likely reduces infant morbidity and mortality.[7,22-24] In targeted high-risk pregnancies, more than half of the severe CHDs are detectable by detailed ultrasound screening and follow-up fetal echocardiography. However, as a population-based screen, routine ultrasound is less accurate than postnatal pediatric echocardiography in detecting CHDs.

With the exception of Central East France and possibly Finland, countries reporting pregnancy termination data to ICBDMS have noted a minimal impact of prenatal diagnosis on the birth prevalence of HLHS (Table 3.2). This is consistent with a 1990-1994 retrospective review conducted by the birth defects surveillance system in Atlanta.[25] However, studies performed in the mid-1990s report a pregnancy termination rate as high as 60% of pregnancies affected with HLHS following prenatal diagnosis.[7,24] Continued close surveillance is required to accurately determine the impact of prenatal diagnosis on complex CHDs.

Preventive Measures

The efficacy of periconceptional multivitamin supplementation (i.e., multivitamins containing folic acid) in reducing the occurrence and recurrence of CHDs — particularly conotruncal heart defects — has been reported from a number of studies.[1,10-12] Consequently, current Canadian efforts to reduce the burden of neural tube defects (NTDs) through increased vitamin supplementation in women of reproductive age and through food fortification with folic acid may also reduce the burden of CHDs.

Prenatal testing is capable, to some extent, of detecting CHDs directly with prenatal ultrasound and fetal echocardiography. Detection of CHDs also occurs by first detecting chromosome abnormalities and, subsequently, their associated CHDs. These measures would provide women with a choice to terminate an affected pregnancy or provide greater management options for the remainder of the pregnancy and the delivery.

Summary

There has been an increasing trend in the total CHD birth prevalence in Canada from 1989 to 1999. Increased ascertainment and an increase in the proportion of births to older women are two possible explanations for this observed trend. The trend in the birth prevalence of an important complex CHD — HLHS — has remained constant. Ongoing surveillance and research are necessary to further understand the epidemiology of CHDs in Canada. Primary prevention of CHDs, the impact of prenatal diagnosis on CHDs and the neonatal management of CHDs are particularly important areas for attention.

References

1. Lin AE, Herring AH, Amstutz KS et al. Cardiovascular Malformations: changes in prevalence and birth status, 1972-1990. *Am J Med Genet* 1999; 84: 102-10.

2. Wen SW, Liu S, Joseph KS, Rouleau J, Allen A. Patterns of infant mortality caused by major congenital anomalies. *Teratology* 2000; 61: 342-6.

3. Roumiana SB, Botton LD, Moore CA et al. Mortality associated with congenital heart defects in the United States. Trends and racial disparities, 1979-1997. *Circulation* 2000; 103: 2376-81.

4. Brackley KJ, Kilby MD, Wright JG et al. Outcome after prenatal diagnosis of hypoplastic left heart syndrome: a case series. *Lancet* 2000; 356: 1143-7.

5. Rogers BT, Msall ME, Buck GM et al. Neurodevelopmental outcome of infants with hypoplastic left heart syndrome. *J Pediatr* 1995; 126: 496-8.

6. Goldberg CS, Schwartz EM, Brunberg JA et al. Neurodevelopmental outcome of patients after the Fontan operation: A comparison between children with hypoplastic left heart syndrome and other functional single ventricle lesions. *J Pediatr* 2000; 137: 646-52.

7. Sharland G, Rollings S, Simpson J, Anderson D. Letter to the Editor. Hypoplastic left heart syndrome. *Lancet* 2001; 357: 722.

8. OMIM (Online Mendelian Inheritance of Man). *Conotruncal heart malformations*. Entry # 217095, 2001. (Available: www3.ncbi.nlm.nih.gov).

9. Harper PS. *Practical Genetic Counselling*, 5th Edition. Boston: Butterworth Heinemann, 1998: 240-6.

10. Botto LD, Khoury MJ, Mulinare J, Erickson JD. Periconceptional multivitamin use and the occurrence of conotruncal heart defects: results from a population-based, case-control study. *Pediatrics* 1996; 98: 911-7.

11. Shaw GM, O'Malley CD, Wasserman CR et al. Maternal periconceptional use of multivitamins and reduced risk for conotruncal heart defects and limb deficiencies among offspring. *Am J Med Genet* 1995; 59: 536-45.

12. Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. *Am J Med Genet* 1996; 62:179-83.

13. O'Rahilly R, Muller F. *Human Embryology and Teratology*, 2nd Edition. Toronto: Wiley-Liss Publications, 1996: 178-87.

14. Botto LD, Loffredo C, Scanlon KS et al. Vitamin A and cardiac outflow tract defects. *Epidemiology* 2001; 12: 491-6.

15. Loffredo CA, Silbergeld EK, Forenz C, Zhang J. Association of transposition of the great areteries in infants with maternal exposures to herbicides and rodenticides. *Am J Epidemiol* 2001; 153: 529-36.

16. Botto LD, Lynberg MC, Erickson JD. Congenital heart defects, maternal febrile illness, and multivitamin use: a population-based study. *Epidemiology* 2001; 12: 485-90.

17. Olshan AF, Schnitzer PG, Baird PA. Paternal age and the risk of congenital heart defects. *Teratology* 1994; 50: 80-4.

18. California Birth Defects Monitoring Program. *Information on heart defects*. 2002. (Available: www.cbdmp.org/).

19. Callif-Daley FA, Huether CA, Edmonds LD. Evaluating false positives in two hospital discharge data sets of the birth defects monitoring program. *Public Health Rep* 1995; 110: 154-60.

20. International Clearinghouse for Birth Defects Monitoring Systems. *Annual Report*. Rome, Italy, 2001.

21. Wen SW, Rouleau J, Lowry RB et al. Congenital anomalies ascertained by two record systems run in parallel in the Canadian province of Alberta. *Can J Public Health* 2000; 91: 193-6.

22. Allan LD, Cook A, Sullivan I, Sharland GK. Hypoplastic left heart syndrome: effects of fetal echocardiography on birth prevalence. *Lancet* 1991; 337: 959-61.

23. Satomi G, Yasukochi S, Shimizu T et al. Has fetal echocardiography improved the prognosis of congenital heart disease? Comparison of patients with hypoplastic left heart syndrome with and without prenatal diagnosis. *Pediatr Int* 1999; 41: 728-32.

24. Brackley KJ, Kilby MD, Wright JG et al. Outcome after prenatal diagnosis of hypoplastic left heart syndrome: a case series. *Lancet* 2000; 356: 1143-7.

25. Montana E, Khoury MJ, Cragan JD, Sharma S, Dhar P, Fyfe D. Trends and outcomes after prenatal diagnosis of congenital cardiac malformations by fetal echocardiography in a well defined birth population, Atlanta, Georgia, 1990-1994. *J Am Coll Cardiol* 1996; 28: 1805-9.

Oral Facial Clefts

Oral facial clefts include two genetically distinct anomalies — cleft lip with or without cleft palate (CL/P) and cleft palate (CP). A CL/P involves the primary palate and encompasses clefts of the lip with or without the palate. A CP involves clefting of the secondary palate only.[1] Approximately 400 to 500 babies are born each year in Canada with a CL/P or CP. Although the appearance of a CL/P or CP at birth can be distressing for new parents, the congenital anomaly is repairable. Surgical correction of the oral facial cleft occurs early in infancy or childhood. With more complex clefts, orthodontia and plastic surgical repairs may continue into adolescence. However, the repair is often complete without chronic health complications. Close monitoring and early intervention to address issues related to dental problems, speech and hearing impairment, as well as potential psychosocial difficulties, optimize the long-term outcome of affected children. The epidemiology of oral facial clefts is highlighted in Table 4.1.

Risk Factors

The lip and primary palate develop at five to seven weeks following conception and the secondary palate completes its formation by eight to twelve weeks following conception.[2] Environmental and genetic factors that disrupt these intricate embryologic processes during this critical period of development result in oral facial clefts.

There are over 200 recognized syndromes, chromosomal or Mendelian in origin, in which oral facial clefts present as one manifestation.[3] After careful clinical exclusion of syndromic causes, the majority of isolated CL/P and CP are considered to be multifactorial in origin. Recurrence risks for isolated CL/P and CP are determined by the severity of the cleft, the number of cases within the family, the sex of the affected child and, in the case of CL/P, the population prevalence of the anomaly.[1]

In the vast majority of cases, there is no identifiable environmental etiology. A number of drugs and environmental agents, however, have been implicated as potential causes of CL/P and CP; cigarette smoking, alcohol and certain medications, including retinoic acid derivatives, phenytoin and trimethadione, have all been reported to increase the risk of oral facial clefts.[4-6] Caffeine has also been suggested as a potential cause, but the majority of epidemiologic studies have not implicated caffeine as a human teratogen.[7]

In some studies, maternal periconceptional supplementation with multivitamins containing folic acid has been reported to reduce the risk of

Table 4.1

Epidemiology of oral facial clefts

Epidemiologic characteristics	Cleft lip with or without cleft palate (CL/P)*	Cleft palate (CP)*
Prevalence rate[1,3,8]	See "Racial distribution" below ~ 50% are CL with an associated CP	1/2.500 ~ 30% are isolated CP
Sex distribution[1,8]	More common in males Ratio ~ 2M:1F; however, sex distribution varies according to race	More common in females Ratio ~ 2F:1M for complete clefts of hard and soft palate and ~ 1F:1M for clefts of soft palate only
Racial distribution[1]	Chinese: 1.7 per 1,000 births Chinese resident in British Columbia: 1.8[9,10] American Indians: 3.6 per 1,000 births British Columbia Indians: 3.7 per 1,000[9,10] Caucasians: 1.5 to 2.0 per 1,000[11]	Prevalence is similar across all races
Etiology[12,13]	Summary of Shprintzen et al.[12] (N= 364)	Summary of Shprintzen et al.[12] (overt CP: N=330)
• presumably multifactorial	54%	41%
• monogenic (syndrome)	13%	20%
• teratogenic	3%	5%
• chromosomal	3%	1%
• disruption or deformation	5%	9%
• unknown	22%	24%
General empiric recurrence risks[3]		
• after one affected child	3%-5%	2%
• with one affected parent	4%	6%
• affected parent and child	10%	15%
Primary prevention with periconceptional multivitamin supplementation containing folic acid[14-16]	Reduction in risk – not consistently reported	Reduction in risk – not consistently reported

*Note: All rates are per total births (live births and stillbirths).

22 31

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

Micromedia
ProQuest

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

oral facial clefts, particularly CL/P. However, the evidence is not conclusive and the exact mechanism of the protective effect is not clear.[14]

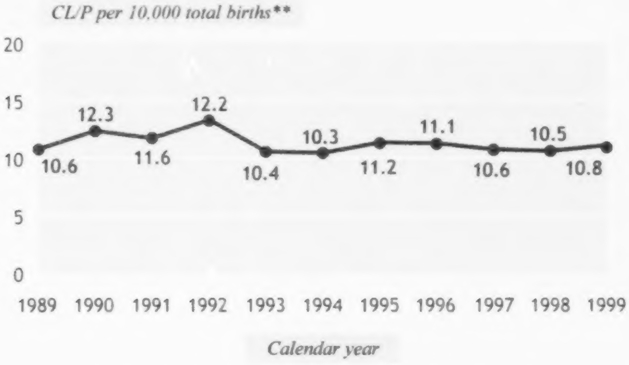
Identified candidate genes for non-syndromic CL/P and CP include: transforming growth factor alpha gene, retinoic acid receptor, methylene tetrahydrofolate reductase (MTHFR) receptor (a genetic variant of an enzyme used in the metabolism of homocysteine), folic acid receptor and the homeobox genes MSX1 and MSX2.[3] Studies on the interaction between at-risk genotypes and environmental factors remain limited.

Prevalence Rate of Oral Facial Clefts in Canada

In 1999 in Canada (all provinces and territories included), 366 infants were born with CL/P, corresponding to a birth prevalence of 10.8 per 10,000 total births (live births and stillbirths). The birth prevalence of CP (all provinces and territories included) was 7.7 per 10,000 total births (261 cases). As depicted in Figures 4.1 and 4.2 (see also Appendix D, Data Table D4.1), the birth prevalence of CL/P and CP in Canada (excluding Nova Scotia) over the 10-year period from 1989-1999 has remained relatively constant.

Figure 4.1

Cleft lip with or without cleft palate (CL/P) rate, *Canada (excluding Nova Scotia),* 1989-1999*



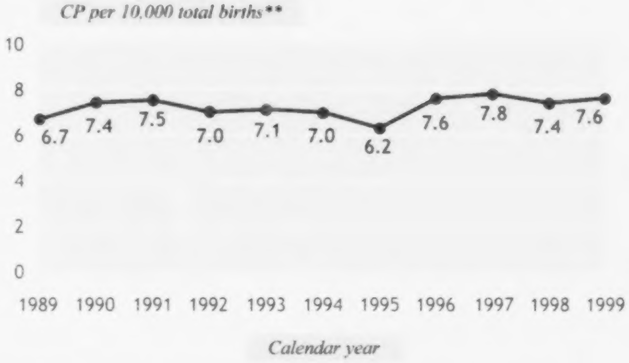
Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

Figure 4.2

Cleft palate (CP) rate, *Canada (excluding Nova Scotia),* 1989-1999*



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

Provincial and Territorial Prevalence Rates

The birth prevalence of CL/P and CP varies considerably across Canada (Figures 4.3 and 4.4; see also Appendix D, Data Tables D4.2 and D4.3). For the combined three-year period of 1997-1999, the provincial/territorial birth prevalence of CL/P ranged from 0 per 10,000 total births in the Yukon to 20.6 per 10,000 total births (32 cases) in Newfoundland. Similarly, the birth prevalence of CP ranged from 0 per 10,000 total births in the Yukon to 12.5 per 10,000 total births (30 cases) in New Brunswick. Although there appears to be considerable variation between the provinces and territories, the small number of cases and the large confidence intervals in the less populated provinces/territories must be taken into account when interpreting these rates.

The variation in the birth prevalence of CL/P in particular may be due, in part, to population differences, such as the proportion of the population who are Aboriginal and at a higher genetic predisposition for CL/P. Certain environmental oral facial clefts, particularly CL/P. However, the evidence is not conclusive and the exact mechanism of the protective effect is not clear.[14]

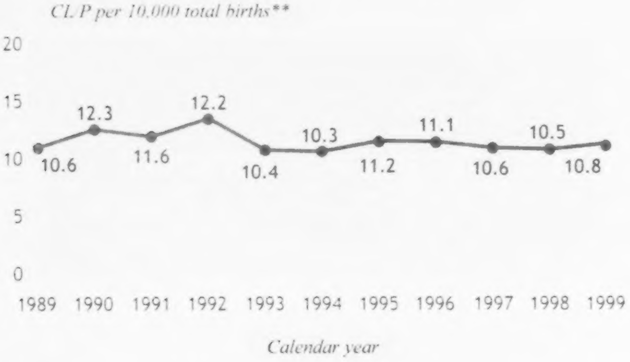
Identified candidate genes for non-syndromic CL/P and CP include: transforming growth factor alpha gene, retinoic acid receptor, methylene tetrahydrofolate reductase (MTHFR) receptor (a genetic variant of an enzyme used in the metabolism of homocysteine), folic acid receptor and the homeobox genes MSX1 and MSX2.[3] Studies on the interaction between at-risk genotypes and environmental factors remain limited.

Prevalence Rate of Oral Facial Clefts in Canada

In 1999 in Canada (all provinces and territories included), 366 infants were born with CL/P, corresponding to a birth prevalence of 10.8 per 10,000 total births (live births and stillbirths). The birth prevalence of CP (all provinces and territories included) was 7.7 per 10,000 total births (261 cases). As depicted in Figures 4.1 and 4.2 (see also Appendix D, Data Table D4.1), the birth prevalence of CL/P and CP in Canada (excluding Nova Scotia) over the 10-year period from 1989-1999 has remained relatively constant.

Figure 4.1

Cleft lip with or without cleft palate (CL/P) rate, *Canada (excluding Nova Scotia),* 1989-1999*



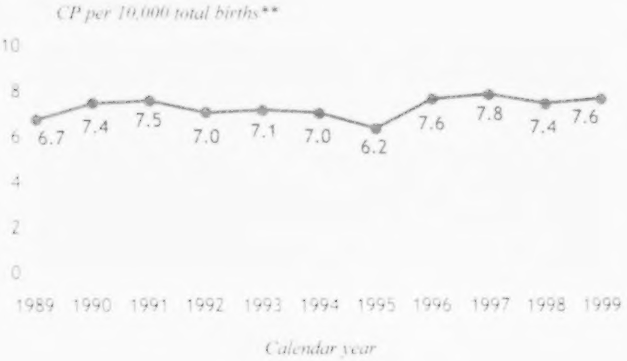
Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

Figure 4.2

Cleft palate (CP) rate, *Canada (excluding Nova Scotia),* 1989-1999*



Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1989-1999

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

Provincial and Territorial Prevalence Rates

The birth prevalence of CL/P and CP varies considerably across Canada (Figures 4.3 and 4.4; see also Appendix D, Data Tables D4.2 and D4.3). For the combined three-year period of 1997-1999, the provincial/territorial birth prevalence of CL/P ranged from 0 per 10,000 total births in the Yukon to 20.6 per 10,000 total births (32 cases) in Newfoundland. Similarly, the birth prevalence of CP ranged from 0 per 10,000 total births in the Yukon to 12.5 per 10,000 total births (30 cases) in New Brunswick. Although there appears to be considerable variation between the provinces and territories, the small number of cases and the large confidence intervals in the less populated provinces/territories must be taken into account when interpreting these rates.

The variation in the birth prevalence of CL/P in particular may be due, in part, to population differences, such as the proportion of the population who are Aboriginal and at a higher genetic predisposition for CL/P. Certain environmental factors, such as variations in folic acid intake, may also contribute to the observed inter-provincial/territorial variation in the birth prevalence of oral facial clefts.

International Comparisons

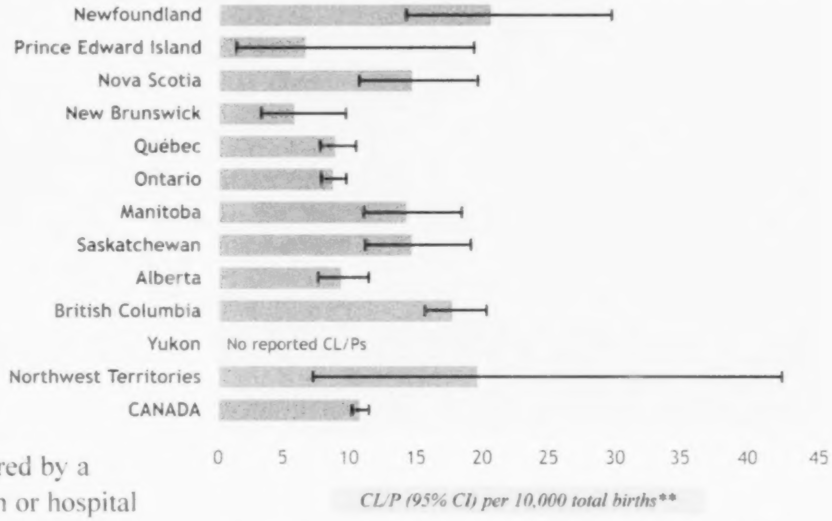
Table 4.2 demonstrates the marked international variation in the rates of oral facial clefts; however, caution is required in interpreting and comparing the rates between countries.[17] Firstly, different ascertainment methods may affect reported rates. For example, a less obvious CP may not be diagnosed until later in infancy at an out-patient clinic and would not be captured by a system that relies on birth notification or hospital discharge records. Secondly, the coding of oral facial clefts can also vary between countries. Some registries with the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) report only isolated oral facial clefts, whereas other surveillance programs, such as CCASS, include all oral facial clefts, even if they are associated with other congenital anomalies.[17]

Impact of Prenatal Diagnosis on Birth Prevalence of Oral Facial Clefts

For isolated oral facial clefts, prenatal testing has had limited impact on birth prevalence rates.[17-20] Parents who are given the diagnosis of an isolated CL/P often elect to continue their pregnancy and, with the counselling and support that are offered, are better prepared when their child is born.

Figure 4.3

Cleft lip with or without cleft palate (CL/P) rate, by province/territory, *Canada, 1997-1999**



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

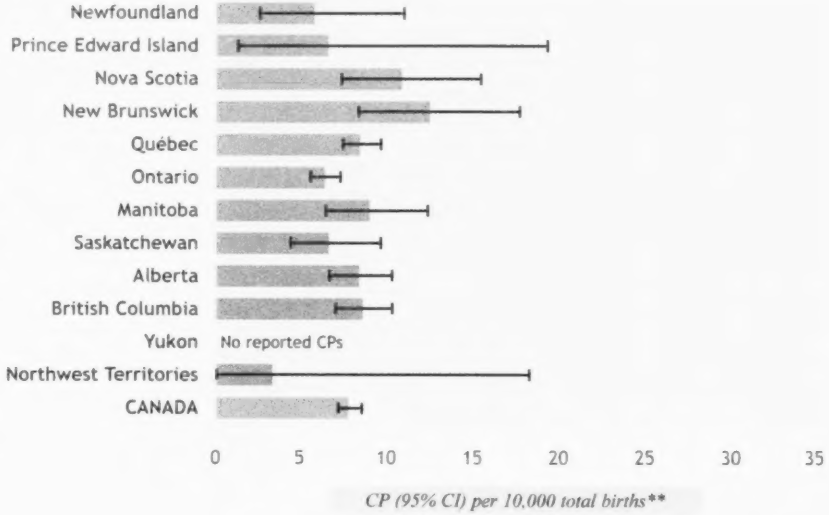
*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI – confidence interval.

Figure 4.4

Cleft palate (CP) rate, by province/territory, *Canada, 1997-1999**



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI – confidence interval.

Table 4.2

Oral facial clefts international rate,* by country/registry, *1999*

Country/registry	Rate of cleft lip with or without cleft palate (CL/P)	Rate of cleft palate (CP)
CANADA	**10.8**	**7.7**
Alberta, Canada	8.9	9.2
Atlanta, USA	8.0	6.7
Central East France	8.4	6.4
England and Wales	6.3	2.9
Hungary	6.2	3.0
Norway	10.5	5.9
South America	14.8	4.3
United Arab Emirates	6.4	7.7

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.[17]
*Per 10,000 total births.

Routine ultrasound screening has very limited success in the prenatal detection of isolated CP because of the shadowing effects and lack of contrast between structures.[18] However, three-dimensional ultrasound imaging and colour doppler may prove useful for prenatal diagnosis of isolated CP.

Prenatal diagnosis of oral facial clefts, particularly CL/P, may have an impact on the birth prevalence in cases where other associated anomalies are detected. For example, congenital heart defects are found in 3%-7% of prenatally detected CL/P cases.[1] When a CL/P is identified by ultrasound in the second trimester, fetal echocardiography and amniocentesis may be considered to rule out associated anomalies. The diagnosis of multiple congenital anomalies, including the presence of an oral facial cleft, may result in termination of pregnancy, with a corresponding reduction in the birth prevalence of this congenital anomaly.

Preventive Measures

There is some evidence to support periconceptional supplementation with multivitamins containing folic acid as a primary preventive measure against oral facial clefts. The suggested risk reduction with this intervention has been reported to be as high as 50% for CL/P and 25% for CP.[14-16] The impact of food fortification with folic acid on the Canadian birth prevalence of oral facial clefts is not yet known. As most cases of CL/P and CP occur to families without identifiable risk factors, there are very few additional primary preventive measures that can be taken, apart from minimizing exposure to possible teratogens such as alcohol and cigarette smoking.

Summary

Oral facial clefts are an important cause of morbidity among Canadian children. The potential for primary prevention based on strategies to increase the consumption of folic acid is promising. Ongoing surveillance of CL/P and CP, combined with focused epidemiologic research, is required to further elucidate the genetic and environmental risk factors associated with CL/P and CP within the Canadian population.

References

1. Gorlin RJ, Cohen MM, Levin LS. Orofacial clefting syndromes: general aspects. In: *Syndromes of the Head and Neck*, 3rd Edition. New York: Oxford University Press, 1990: chapter 20, 693-700.
2. Moore KL, Persaud TVN. *The Developing Human. Clinically Oriented Embryology*, 6th Edition. Toronto: W.B. Saunders Company, 1998: 245-52.
3. OMIM (Online Mendelian Inheritance of Man). *Orofacial cleft*. Entry #19530, 2001. *Cleft palate*. Entry #119540, 2001. (Available: www3.ncbi.nlm.nih.gov).

factors, such as variations in folic acid intake, may also contribute to the observed inter-provincial/territorial variation in the birth prevalence of oral facial clefts.

International Comparisons

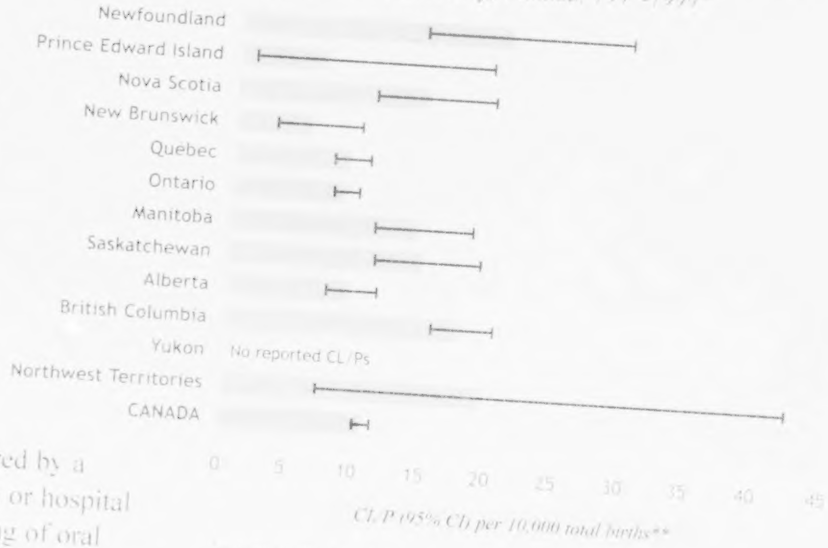
Table 4.2 demonstrates the marked international variation in the rates of oral facial clefts; however, caution is required in interpreting and comparing the rates between countries.[17] Firstly, different ascertainment methods may affect reported rates. For example, a less obvious CP may not be diagnosed until later in infancy at an out-patient clinic and would not be captured by a system that relies on birth notification or hospital discharge records. Secondly, the coding of oral facial clefts can also vary between countries. Some registries with the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) report only isolated oral facial clefts, whereas other surveillance programs, such as CCASS, include all oral facial clefts, even if they are associated with other congenital anomalies.[7]

Impact of Prenatal Diagnosis on Birth Prevalence of Oral Facial Clefts

For isolated oral facial clefts, prenatal testing has had limited impact on birth prevalence rates.[17-20] Parents who are given the diagnosis of an isolated CL/P often elect to continue their pregnancy and, with the counselling and support that are offered, are better prepared when their child is born.

Figure 4.3

Cleft lip with or without cleft palate (CL/P) rate, by province/territory, *Canada, 1997-1999**



Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1997-1999.

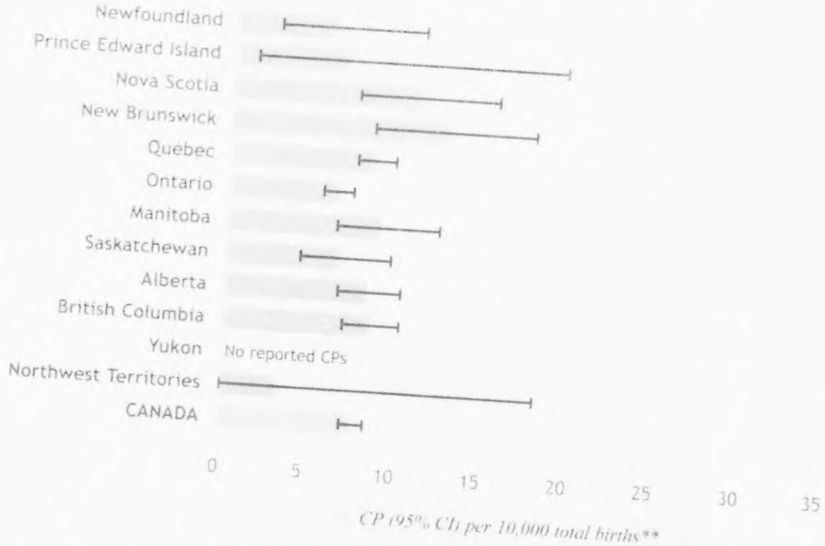
*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI confidence interval.

Figure 4.4

Cleft palate (CP) rate, by province/territory, *Canada, 1997-1999**



Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI confidence interval.

Table 4.2

Oral facial clefts international rate,* by country/registry, *1999*

Country/registry	Rate of cleft lip with or without cleft palate (CL/P)	Rate of cleft palate (CP)
CANADA	10.8	7.7
Alberta, Canada	8.9	9.2
Atlanta, USA	8.0	6.7
Central East France	8.4	6.4
England and Wales	6.3	2.9
Hungary	6.2	3.0
Norway	10.5	5.9
South America	14.8	4.3
United Arab Emirates	6.4	7.7

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.

*Per 10,000 total births.

Routine ultrasound screening has very limited success in the prenatal detection of isolated CP because of the shadowing effects and lack of contrast between structures.[18] However, three-dimensional ultrasound imaging and colour doppler may prove useful for prenatal diagnosis of isolated CP.

Prenatal diagnosis of oral facial clefts, particularly CL/P, may have an impact on the birth prevalence in cases where other associated anomalies are detected. For example, congenital heart defects are found in 3%-7% of prenatally detected CL/P cases.[1] When a CL/P is identified by ultrasound in the second trimester, fetal echocardiography and amniocentesis may be considered to rule out associated anomalies. The diagnosis of multiple congenital anomalies, including the presence of an oral facial cleft, may result in termination of pregnancy, with a corresponding reduction in the birth prevalence of this congenital anomaly.

Preventive Measures

There is some evidence to support periconceptional supplementation with multivitamins containing folic acid as a primary preventive measure against oral facial clefts. The suggested risk reduction with this intervention has been reported to be as high as 50% for CL/P and 25% for CP.[14-16] The impact of food fortification with folic acid on the Canadian birth prevalence of oral facial clefts is not yet known. As most cases of CL/P and CP occur to families without identifiable risk factors, there are very few additional primary preventive measures that can be taken, apart from minimizing exposure to possible teratogens such as alcohol and cigarette smoking.

Summary

Oral facial clefts are an important cause of morbidity among Canadian children. The potential for primary prevention based on strategies to increase the consumption of folic acid is promising. Ongoing surveillance of CL/P and CP, combined with focused epidemiologic research, is required to further elucidate the genetic and environmental risk factors associated with CL/P and CP within the Canadian population.

References

1. Gorlin RJ, Cohen MM, Levin LS. Orofacial clefting syndromes: general aspects. In: *Syndromes of the Head and Neck*, 3rd Edition. New York: Oxford University Press, 1990: chapter 20, 693-700.

2. Moore KL, Persaud TVN. *The Developing Human. Clinically Oriented Embryology*, 6th Edition. Toronto: W.B. Saunders Company, 1998: 245-52.

3. OMIM (Online Mendelian Inheritance of Man). *Orofacial cleft*. Entry #19530, 2001. *Cleft palate*. Entry #119540, 2001. (Available: www3.ncbi.nlm.nih.gov).

4. Jones KL. Environmental Agents: Fetal Alcohol Syndrome. Fetal Hydantoin Syndrome. Fetal Trimethadione Syndrome. Retinoic Acid Embryopathy. In: *Smith's Recognizable Patterns of Human Development*, 5th Edition. Toronto: W.B. Saunders Company, 1997: 555-73.

5. Shaw GM, Wasserman CR, Lammer EJ et al. Orofacial clefts, parental cigarette smoking, and transforming growth factor-alpha gene variants. *Am J Hum Genet* 1996; 58: 551-6.

6. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. *Am J Med Genet* 1999; 3: 242-4.

7. Christian MS, Brent RL. Teratogen update: evaluation of the reproductive and developmental risks of caffeine. *Teratology* 2001; 64: 51-78.

8. Cohen MM, Gorlin RJ, Fraser FC. Craniofacial Disorders. In: Emery A, Rimoin D (Eds.), *Principles and Practice of Medical Genetics*, 3rd Edition. New York: Churchill Livingstone, 1997: 1121-47.

9. Lowry RB, Renwick DHG. Incidence of cleft lip and palate in British Columbia Indians. *J Med Genet* 1969; 1: 67-9.

10. Lowry RB, Trimble BK. Incidence rates for cleft lip and palate in British Columbia 1952-71 for North American Indian, Japanese, Chinese and total populations: secular trends over twenty years. *Teratology* 1977; 3: 277-83.

11. Mossey PA, Little J. Epidemiology of oral clefts: an international perspective. In: *Cleft Lip and Palate. From Origin to Treatment*. Oxford University Press (in press, 2002).

12. Shprintzen RJ, Siegel-Sadewitz VL, Amato J et al. Anomalies associated with cleft lip, cleft palate, or both. *Am J Med Genet* 1985; 20: 585.

13. Lettieri J. Lips and Oral Cavity. In: Stevenson RE, Hall JG, Goodman RM (Eds.), *Human Malformations and Related Anomalies*. Vol. 2. New York: Oxford University Press, 1993: 367-81.

14. Itikala PR, Watkins ML, Mulinare J, Moore CA, Liu Y. Maternal multivitamin use and orofacial clefts in offspring. *Teratology* 2001; 63: 79-86.

15. Tolarova M, Harris J. Reduced recurrence of orofacial clefts after periconceptional supplementation with high dose folic acid and multivitamins. *Teratology* 1995; 51: 71-8.

16. Shaw GM, Lammer EJ, Wasserman CR, O'Malley CD, Tolarova MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. *Lancet* 1995; 346: 393-6.

17. International Clearinghouse for Birth Defects Monitoring Systems. *Annual Report*. Rome, Italy, 2001.

18. Babock C. The fetal face and neck. In: Callen PW (Ed.), *Ultrasonography in Obstetrics and Gynecology*, 4th Edition. New York: W.B. Saunders Company, 2000: 307-27.

19. Hafner E, Steriste W, Scholler J et al. Prenatal diagnosis of fetal malformations. *Prenat Diagn* 1997; 17: 51-8.

20. Sohan K, Freer M, Mercer N et al. Prenatal detection of facial clefts. *Fetal Diagn Ther* 2001; 4: 196-9.

5

Limb Reduction Defects

Limb reduction defects (LRDs), more commonly known as congenital amputation(s), are relatively rare and heterogeneous musculoskeletal anomalies characterized by the total or partial absence of an arm or a leg or a smaller component, for example, a finger or a toe.[1] Despite being so rare, the history of LRDs as it relates to the surveillance of congenital anomalies is an important one. The development of congenital anomalies surveillance activities worldwide was a direct result of the thalidomide experience in the late 1950s and early 1960s.

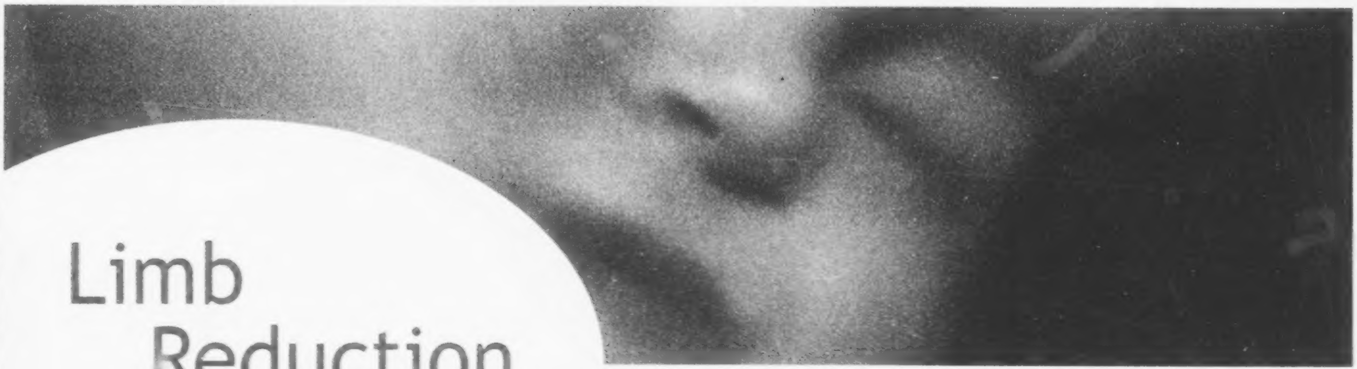
The reported birth prevalence of LRDs varies considerably as the rates are influenced by various factors such as the case definition.[2]

Approximately 3 to 8 infants per 10,000 live births are affected with an LRD,[1,3,4] and at least 30% of all LRDs are associated with additional congenital anomalies.[5,6] Infant mortality and morbidity are considerably increased if coupled with a serious anomaly, such as a cardiac or gastrointestinal defect

The events of the thalidomide tragedy took place between 1956 and 1965. The drug thalidomide was synthesized and first marketed in Germany and widely prescribed thereafter. Dr. Widukind Lenz, then a geneticist at the University of Hamburg, was the first person to establish the causal association between thalidomide and its characteristic facial and limb embryopathy. The first case he described was in 1956, and within one year 3,049 cases were reported in Germany alone.[7]

Epidemics of thalidomide embryopathy were subsequently reported in several countries throughout the world between 1959 and 1961. The drug was withdrawn from commercial sale in several European markets in the latter part of 1961.[7,8] In Canada, thalidomide was legally available between April 1961 and March 1962. An estimated 122 cases of thalidomide embryopathy were confirmed in Canada alone during this brief time period.[7,8]

The true number of thalidomide embryopathy cases is not known as many early newborn deaths (depending on the country, reported neonatal and infant mortality rate varied from 40%-80%) may not have been included as cases.[7] Furthermore, the estimates are likely to be confounded by the baseline LRD birth prevalence.



Limb Reduction Defects

Limb reduction defects (LRDs), more commonly known as congenital amputation(s), are relatively rare and heterogeneous musculoskeletal anomalies characterized by the total or partial absence of an arm or a leg or a smaller component, for example, a finger or a toe.[1] Despite being so rare, the history of LRDs as it relates to the surveillance of congenital anomalies is an important one. The development of congenital anomalies surveillance activities worldwide was a direct result of the thalidomide experience in the late 1950s and early 1960s.

The reported birth prevalence of LRDs varies considerably as the rates are influenced by various factors such as the case definition.[2]

Approximately 3 to 8 infants per 10,000 live births are affected with an LRD,[1,3,4] and at least 30% of all LRDs are associated with additional congenital anomalies.[5,6] Infant mortality and morbidity are considerably increased if coupled with a serious anomaly, such as a cardiac or gastrointestinal defect.

Inconsistent classification of LRDs has created challenges in the surveillance and epidemiologic research of these anomalies. Definitions based on morphogenesis and pathogenesis have been used, but are not universally accepted and do not clearly translate into the standard International Classification of Diseases (ICD) codes.[10] The Classification Committee of the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) proposed a descriptive classification system, distinguishing anomalies into three basic types: deficiencies, supernumerary structures and fusion/separation defects.[11,12]

Transverse limb anomalies are the most common LRDs.[12] Upper limb anomalies are at least twice as common as lower LRDs, and unilateral defects occur more frequently than bilateral defects among live born cases.[1,8] In contrast, upper limb defects are less frequent and associated anomalies are more common among stillbirth cases.[13]

Risk Factors

The critical period of limb development occurs 28 to 56 days following conception.[14,15] The pathogenic mechanisms that disrupt the development of the limbs are not clearly understood. Furthermore, the etiology of specific LRDs is not revealed by the anatomic defect itself, as the same LRD may have several different causes.[1,6]

Limb reduction defects occur in isolation or in association with chromosome abnormalities, single gene mutations and genetic syndromes.[4,16] When genetic and environmental teratogenic causes are excluded, many LRDs are believed to have a multifactorial origin with low recurrence risks.[16]

With the exception of thalidomide, relatively few LRDs can be conclusively attributed to teratogenic agents.[17] The critical period of sensitivity to thalidomide embryopathy is between 20 and 36 days following conception.[18] Approximately 20% of pregnancies exposed during this period will result in children with thalidomide embryopathy, which includes an array of LRDs, as well as other major congenital malformations.[18,19]

Cases of limb defects have also been reported among women exposed to aminopterin and methotrexate, but the numbers are too small to conclusively demonstrate an association.[19] Mild terminal digit defects have been reported with first trimester exposure to warfarin and hydantoin.[1] Transverse LRDs have also been reported in children of women exposed to misoprostol during unsuccessful abortion efforts.[19] Finally, isotretinoin, a therapeutic product for acne, has been implicated in the etiology of some LRDs.[19,20]

Common LRD Terms

amelia – complete absence of an upper or lower limb (limb girdle not affected)[1]

hemimelia – absence of the distal half of a limb[14]

intercalary deficiency – absence or severe hypoplasia of the proximal part of the limb (humerus or femur, radius, ulna, tibia or fibula, also in combination) with distal segment (hand and foot) normal or nearly normal[1]

meromelia – partial absence of a free limb[1]

phocomelia – the hands or feet appear to be attached more or less directly to the trunk[14]

postaxial deficiency – absence or partial absence of the fifth finger, fifth metacarpal or ulna; or the fifth toe, fifth metatarsal or fibula[1]

preaxial deficiency – absence or partial absence of the thumb, first metacarpal or radius; or the hallux, first metatarsal or tibia[1]

transverse limb anomaly – absence of the distal structures of an arm or leg, that extends across the whole width of the limb; the proximal structures are normal or can be deficient[12]

The potential association of LRDs, primarily transverse limb deficiencies, with exposure to early first trimester chorionic villus sampling (CVS) has been extensively explored through various programs and registries and remains controversial.[21-28] A voluntary international CVS registry managed by the World Health Organization found no evidence to suggest an increased risk for LRDs over the background population risk when CVS was performed in the later part of the first trimester.[25,26] As the absolute risk of LRDs associated with CVS is unknown, particularly if the procedure is performed before eight to nine weeks in pregnancy, most centres practise on the side of caution by offering the procedure later in the first trimester of pregnancy.[29]

Maternal smoking has been implicated, although not consistently, as a risk factor for LRDs.[30-33] A vascular disruptive event has been postulated as the mechanism for the teratogenic effects of smoking.[33] Reports of environmental pollution and LRDs have also been published but the association has not been conclusively demonstrated.[34,35] Other maternal health conditions, such as poorly controlled diabetes and varicella infection during pregnancy, can result in multiple congenital anomalies that may include LRDs.[1]

A common mutation — C677T of the methylene tetrahydrofolate reductase gene (MTHFR), an enzyme used in homocysteine metabolism — has been associated with the occurrence of neural tube defects (NTDs). Periconceptional folic acid supplementation may improve enzyme function and reduce the risk of NTDs in offspring. More recent evidence suggests a protective effect against LRDs with periconceptional folic acid-containing multivitamin supplementation.[36,37] Furthermore, a recent case report suggested that the presence of MTHFR homozygosity may be a predisposing factor for the development of terminal transverse LRDs.[38]

Prevalence Rate of Limb Reduction Defects in Canada

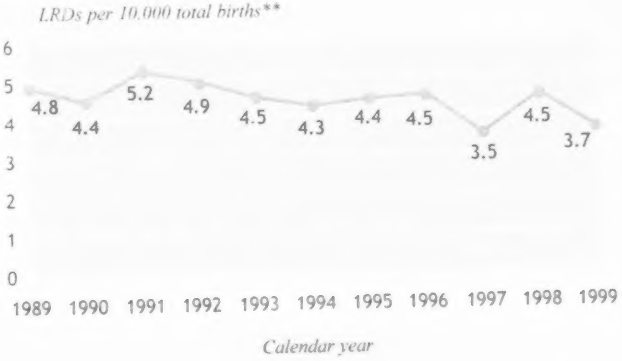
In Canada in 1999 (all provinces and territories included), the birth prevalence of LRDs was 3.6 per 10,000 total births (live births and stillbirths) or 123 cases. There has been a marked decline in the birth prevalence of LRDs in Canada (excluding Nova Scotia) from 1989-1999 (Figure 5.1; see also Appendix D, Data Table D5.1). The exact cause for this decline is unknown. The observed trend may be due, in part, to the prenatal diagnosis and termination of pregnancies affected by LRDs, particularly if associated with other serious congenital anomalies.

Provincial and Territorial Prevalence Rates

Provincial and territorial birth prevalence rates over the combined three years from 1997-1999 are shown in Figure 5.2 (see also Appendix D, Data Table D5.2). The birth prevalence among the provinces and territories over this three-year time period varied considerably. No cases were reported in Prince Edward Island, and only one case was identified in each of Yukon and Northwest Territories.

Figure 5.1

Limb reduction defect (LRD) rate,
Canada (excluding Nova Scotia), 1989-1999*



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.
*Nova Scotia is excluded because data are not available for all years.
**Total births include live births and stillbirths.

Inconsistent classification of LRDs has created challenges in the surveillance and epidemiologic research of these anomalies. Definitions based on morphogenesis and pathogenesis have been used, but are not universally accepted and do not clearly translate into the standard International Classification of Diseases (ICD) codes.[10] The Classification Committee of the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) proposed a descriptive classification system, distinguishing anomalies into three basic types: deficiencies, supernumerary structures and fusion/separation defects.[11,12]

Transverse limb anomalies are the most common LRDs.[12] Upper limb anomalies are at least twice as common as lower LRDs, and unilateral defects occur more frequently than bilateral defects among live born cases.[1,8] In contrast, upper limb defects are less frequent and associated anomalies are more common among stillbirth cases.[13]

Risk Factors

The critical period of limb development occurs 28 to 56 days following conception.[14,15] The pathogenic mechanisms that disrupt the development of the limbs are not clearly understood. Furthermore, the etiology of specific LRDs is not revealed by the anatomic defect itself, as the same LRD may have several different causes.[1,6]

Limb reduction defects occur in isolation or in association with chromosome abnormalities, single gene mutations and genetic syndromes.[4,16] When genetic and environmental teratogenic causes are excluded, many LRDs are believed to have a multifactorial origin with low recurrence risks.[16]

With the exception of thalidomide, relatively few LRDs can be conclusively attributed to teratogenic agents.[17] The critical period of sensitivity to thalidomide embryopathy is between 20 and 36 days following conception.[18] Approximately 20% of pregnancies exposed during this period will result in children with thalidomide embryopathy, which includes an array of LRDs, as well as other major congenital malformations.[18,19]

Cases of limb defects have also been reported among women exposed to aminopterin and methotrexate, but the numbers are too small to conclusively demonstrate an association.[19] Mild terminal digit defects have been reported with first trimester exposure to warfarin and hydantoin.[1] Transverse LRDs have also been reported in children of women exposed to misoprostol during unsuccessful abortion efforts.[19] Finally, isotretinoin, a therapeutic product for acne, has been implicated in the etiology of some LRDs.[19,20]

Common LRD Terms

amelia – complete absence of an upper or lower limb (limb girdle not affected)[1]

hemimelia – absence of the distal half of a limb[14]

intercalary deficiency – absence or severe hypoplasia of the proximal part of the limb (humerus or femur, radius, ulna, tibia or fibula, also in combination) with distal segment (hand and foot) normal or nearly normal[1]

meromelia – partial absence of a free limb[1]

phocomelia – the hands or feet appear to be attached more or less directly to the trunk[14]

postaxial deficiency – absence or partial absence of the fifth finger, fifth metacarpal or ulna; or the fifth toe, fifth metatarsal or fibula[1]

preaxial deficiency – absence or partial absence of the thumb, first metacarpal or radius; or the hallux, first metatarsal or tibia[1]

transverse limb anomaly – absence of the distal structures of an arm or leg, that extends across the whole width of the limb; the proximal structures are normal or can be deficient[12]

The potential association of LRDs, primarily transverse limb deficiencies, with exposure to early first trimester chorionic villus sampling (CVS) has been extensively explored through various programs and registries and remains controversial.[21-28] A voluntary international CVS registry managed by the World Health Organization found no evidence to suggest an increased risk for LRDs over the background population risk when CVS was performed in the later part of the first trimester.[25,26] As the absolute risk of LRDs associated with CVS is unknown, particularly if the procedure is performed before eight to nine weeks in pregnancy, most centres practise on the side of caution by offering the procedure later in the first trimester of pregnancy.[29]

Maternal smoking has been implicated, although not consistently, as a risk factor for LRDs.[30-33] A vascular disruptive event has been postulated as the mechanism for the teratogenic effects of smoking.[33] Reports of environmental pollution and LRDs have also been published but the association has not been conclusively demonstrated.[34,35] Other maternal health conditions, such as poorly controlled diabetes and varicella infection during pregnancy, can result in multiple congenital anomalies that may include LRDs.[1]

A common mutation — C677T of the methylene tetrahydrofolate reductase gene (MTHFR), an enzyme used in homocysteine metabolism — has been associated with the occurrence of neural tube defects (NTDs). Periconceptional folic acid supplementation may improve enzyme function and reduce the risk of NTDs in offspring. More recent evidence suggests a protective effect against LRDs with periconceptional folic acid-containing multivitamin supplementation.[36,37] Furthermore, a recent case report suggested that the presence of MTHFR homozygosity may be a predisposing factor for the development of terminal transverse LRDs.[38]

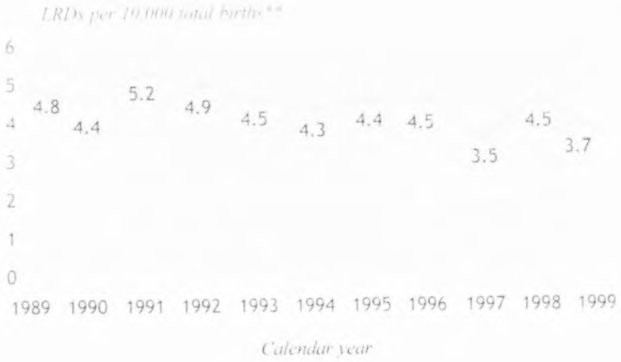
Prevalence Rate of Limb Reduction Defects in Canada

In Canada in 1999 (all provinces and territories included), the birth prevalence of LRDs was 3.6 per 10,000 total births (live births and stillbirths) or 123 cases. There has been a marked decline in the birth prevalence of LRDs in Canada (excluding Nova Scotia) from 1989-1999 (Figure 5.1; see also Appendix D, Data Table D5.1). The exact cause for this decline is unknown. The observed trend may be due, in part, to the prenatal diagnosis and termination of pregnancies affected by LRDs, particularly if associated with other serious congenital anomalies.

Provincial and territorial birth prevalence rates over the combined three years from 1997-1999 are shown in Figure 5.2 (see also Appendix D, Data Table D5.2). The birth prevalence among the provinces and territories over this three-year time period varied considerably. No cases were reported in Prince Edward Island, and only one case was identified in each of Yukon and Northwest Territories.

Figure 5.1

Limb reduction defect (LRD) rate,
Canada (excluding Nova Scotia), 1989-1999*



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

**Total births include live births and stillbirths.

The remaining provinces reported rates from 1.7 per 10,000 total births in New Brunswick (95% CI: 0.4-4.3) to 6.6 per 10,000 total births in Saskatchewan (95% CI: 4.3-9.7).

The Alberta birth prevalence of LRDs reported by the Canadian Congenital Anomalies Surveillance System (CCASS) was 4.4 per 10,000 total births for 1997-1999. In contrast, the Alberta Congenital Anomalies Surveillance System (ACASS) reported birth prevalence rates for Alberta of 6.2, 8.7 and 12.9 for 1997, 1998 and 1999, respectively.[39] This disparity is likely due to differences in coding guidelines; CCASS reports the number of affected stillbirths and live births and does not report more than one limb reduction anomaly per case. ACASS reports the total number of LRDs observed, even if more than one LRD is reported from a single case.

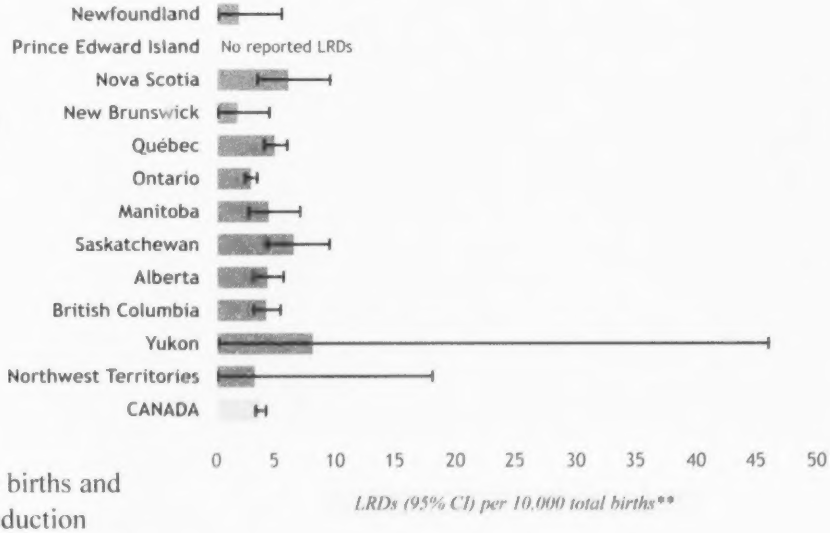
International Comparisons

Comparisons of LRD rates for Canada and several other countries and registries are depicted in Table 5.1. Canada's 1999 rate of 3.6 per 10,000 total births is comparable to rates from registries in Atlanta (USA), Norway and Central East France. The international variations observed are likely due, in part, to differences in ascertainment and the coding guidelines followed. Alberta's LRD birth prevalence is the highest of the rates presented and is likely due to coding procedures, as previously described.

Although the numbers are small, there have been ongoing occurrences of thalidomide embryopathy reported in the 1990s in developing countries. These cases occur where thalidomide is used to treat leprosy and where drug control measures are more relaxed.[18,40]

Figure 5.2

Limb reduction defect (LRD) rate, by province/territory, Canada, 1997-1999*



Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI – confidence interval.

Impact of Prenatal Diagnosis on Birth Prevalence of Limb Reduction Defects

Major limb deficiencies can be diagnosed prenatally by second trimester ultrasound. The reported detection rate for isolated LRDs varies from 20%-64%, depending upon the type of LRD, the presence of other major anomalies and ultrasound screening policies.[41] As evident in Table 5.1, there is some variation in the impact of prenatal diagnosis on the birth prevalence of LRDs internationally.

Preventive Measures

Avoidance of potential teratogens, such as specific medications and cigarette smoking, is a prudent primary preventive measure against LRDs. A protective effect of periconceptional folic acid-containing multivitamin supplementation has been suggested. Ongoing surveillance of LRDs in Canada will be required to examine any impact of vitamin supplementation or folic acid food fortification.

Table 5.1

Limb reduction defect (LRD) international rate,* by country/registry, *1999*

Country/registry	LRD in live births and stillbirths	LRD in live births, stillbirths and TOP
CANADA	**3.6**	**N/A**
Alberta, Canada	12.9	14.4
Atlanta, USA	3.6	N/A
Australia**	4.7	5.8
Central East France	3.4	4.4
England and Wales	3.3	3.4
Finland	5.7	6.2
Hungary	2.2	2.2
Norway	3.7	5.0
South America	6.2	N/A
United Arab Emirates	3.9	N/A

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.[11]
*Per 10,000 total births.
**1998 data.
TOP – terminations of pregnancy.
N/A – not available.

Summary

The thalidomide tragedy, as well as concerns about an association between fetal limb defects and CVS, has highlighted the importance of congenital anomalies surveillance activities. Ongoing surveillance may also play a key role in further delineating the etiology of LRDs.

References

1. Stevenson RE, Meyer LC. The limbs. In: Stevenson RE, Hall JG, Goodman RM (Eds.), *Human Malformations and Related Anomalies.* Vol. II. New York: Oxford University Press, 1993: 703-20.
2. Kelsey JL. *Epidemiology of Musculoskeletal Disorders*. New York: Oxford University Press, 1982: 36-47.
3. McGuirk CK, Westgate M, Holmes LB. Limb deficiencies in newborn infants. *Pediatrics* 2001; 108: 1-7. (Available: www.pediatrics.org/cgi/content/full/108/4/e64).
4. Froster-Iskenius UG, Baird PA. Limb reduction defects in over one million consecutive livebirths. *Teratology* 1989; 39: 127-35.
5. Kallen B, Rahmani TMZ, Winberg J. Infants with congenital limb reduction registered in the Swedish Register of Congenital Malformations. *Teratology* 1984; 29: 73-85.
6. Rosano A, Botto LD, Olney RS et al. Limb defects associated with major congenital anomalies: clinical and epidemiological study from the International Clearinghouse for Birth Defects Monitoring Systems. *Am J Med Genet* 2000; 93: 110-6.
7. Lenz W. A short history of thalidomide embryopathy. *Teratology* 1988; 38: 203-15.
8. Wertelecki W. International Birth Defects Information Systems: Special Thalidomide Edition. 1999. (Available: http://ibis-birthdefects.org/start/genothal.htm.).
9. Thalidomide Victims Association of Canada. 2002. (Available: www. thalidomide.ca/english/wit.html).
10. Froster UG. Academicians are more likely to share each other's toothbrush than each other's nomenclature [Cohen, 1982]. *Am J Med Genet* 1996; 66: 471-4.
11. International Clearinghouse for Birth Defects Monitoring Systems. *Annual Report*. Rome, Italy, 2001.
12. Stoll C. Letter to the Editor. Classification of limb defects. *Am J Med Genet* 1998; 77: 439-41.
13. Froster UG. Baird PA. Congenital defects of the limbs in stillbirths: data from a population-based study. *Am J Med Genet* 1993; 46: 479-82.
14. O'Rahilly R, Muller F. *Human Embryology and Teratology*, 2nd Edition. Toronto: Wiley-Liss Publications, 1996: 349-60.

The remaining provinces reported rates from 1.7 per 10,000 total births in New Brunswick (95% CI: 0.4-4.3) to 6.6 per 10,000 total births in Saskatchewan (95% CI: 4.3-9.7).

The Alberta birth prevalence of LRDs reported by the Canadian Congenital Anomalies Surveillance System (CCASS) was 4.4 per 10,000 total births for 1997-1999. In contrast, the Alberta Congenital Anomalies Surveillance System (ACASS) reported birth prevalence rates for Alberta of 6.2, 8.7 and 12.9 for 1997, 1998 and 1999, respectively.[39] This disparity is likely due to differences in coding guidelines: CCASS reports the number of affected stillbirths and live births and does not report more than one limb reduction anomaly per case. ACASS reports the total number of LRDs observed, even if more than one LRD is reported from a single case.

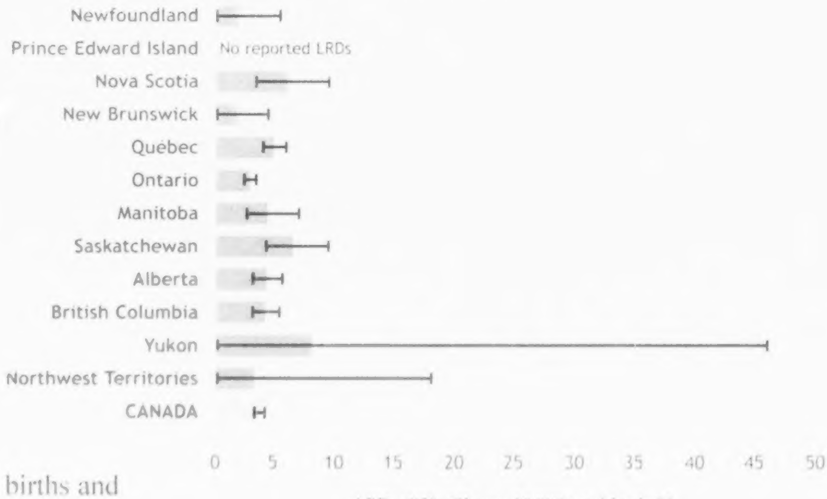
International Comparisons

Comparisons of LRD rates for Canada and several other countries and registries are depicted in Table 5.1. Canada's 1999 rate of 3.6 per 10,000 total births is comparable to rates from registries in Atlanta (USA), Norway and Central East France. The international variations observed are likely due, in part, to differences in ascertainment and the coding guidelines followed. Alberta's LRD birth prevalence is the highest of the rates presented and is likely due to coding procedures, as previously described.

Although the numbers are small, there have been ongoing occurrences of thalidomide embryopathy reported in the 1990s in developing countries. These cases occur where thalidomide is used to treat leprosy and where drug control measures are more relaxed.[18,40]

Figure 5.2

Limb reduction defect (LRD) rate, by province/ territory, *Canada, 1997-1999**



Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

**Total births include live births and stillbirths.

CI — confidence interval.

Impact of Prenatal Diagnosis on Birth Prevalence of Limb Reduction Defects

Major limb deficiencies can be diagnosed prenatally by second trimester ultrasound. The reported detection rate for isolated LRDs varies from 20%-64%, depending upon the type of LRD, the presence of other major anomalies and ultrasound screening policies.[41] As evident in Table 5.1, there is some variation in the impact of prenatal diagnosis on the birth prevalence of LRDs internationally.

Preventive Measures

Avoidance of potential teratogens, such as specific medications and cigarette smoking, is a prudent primary preventive measure against LRDs. A protective effect of periconceptional folic acid-containing multivitamin supplementation has been suggested. Ongoing surveillance of LRDs in Canada will be required to examine any impact of vitamin supplementation or folic acid food fortification.

Table 5.1

Limb reduction defect (LRD) international rate,* by country/registry, *1999*

Country/registry	LRD in live births and stillbirths	LRD in live births, stillbirths and TOP
CANADA	3.6	N/A
Alberta, Canada	12.9	14.4
Atlanta, USA	3.6	N/A
Australia**	4.7	5.8
Central East France	3.4	4.4
England and Wales	3.3	3.4
Finland	5.7	6.2
Hungary	2.2	2.2
Norway	3.7	5.0
South America	6.2	N/A
United Arab Emirates	3.9	N/A

Source: International Clearinghouse for Birth Defects Monitoring Systems, 2001.[11]

*Per 10,000 total births.

**1998 data.

TOP = terminations of pregnancy.

N/A = not available.

Summary

The thalidomide tragedy, as well as concerns about an association between fetal limb defects and CVS, has highlighted the importance of congenital anomalies surveillance activities. Ongoing surveillance may also play a key role in further delineating the etiology of LRDs.

References

1. Stevenson RE, Meyer LC. The limbs. In: Stevenson RE, Hall JG, Goodman RM (Eds.), *Human Malformations and Related Anomalies*. Vol. II. New York: Oxford University Press, 1993: 703-20.
2. Kelsey JL. *Epidemiology of Musculoskeletal Disorders*. New York: Oxford University Press, 1982: 36-47.
3. McGuirk CK, Westgate M, Holmes LB. Limb deficiencies in newborn infants. *Pediatrics* 2001; 108: 1-7. (Available: www.pediatrics.org/cgi/content/full/108/4/e64).
4. Froster-Iskenius UG, Baird PA. Limb reduction defects in over one million consecutive livebirths. *Teratology* 1989; 39: 127-35.
5. Kallen B, Rahmani TMZ, Winberg J. Infants with congenital limb reduction registered in the Swedish Register of Congenital Malformations. *Teratology* 1984; 29: 73-85.
6. Rosano A, Botto LD, Olney RS et al. Limb defects associated with major congenital anomalies: clinical and epidemiological study from the International Clearinghouse for Birth Defects Monitoring Systems. *Am J Med Genet* 2000; 93: 110-6.
7. Lenz W. A short history of thalidomide embryopathy. *Teratology* 1988; 38: 203-15.
8. Wertelecki W. International Birth Defects Information Systems: Special Thalidomide Edition. 1999. (Available: http://ibis-birthdefects.org/start/genothal.htm.).
9. Thalidomide Victims Association of Canada. 2002. (Available: www.thalidomide.ca/english/wit.html).
10. Froster UG. Academicians are more likely to share each other's toothbrush than each other's nomenclature [Cohen, 1982]. *Am J Med Genet* 1996; 66: 471-4.
11. International Clearinghouse for Birth Defects Monitoring Systems. *Annual Report*. Rome, Italy, 2001.
12. Stoll C. Letter to the Editor. Classification of limb defects. *Am J Med Genet* 1998; 77: 439-41.
13. Froster UG, Baird PA. Congenital defects of the limbs in stillbirths: data from a population-based study. *Am J Med Genet* 1993; 46: 479-82.
14. O'Rahilly R, Muller F. *Human Embryology and Teratology*, 2nd Edition. Toronto: Wiley-Liss Publications, 1996: 349-60.

15. Moore KL, Persaud TVN. *The Developing Human. Clinically Oriented Embryology*, 6th Edition. Toronto: W.B. Saunders Company, 1998: chapter 17, 433-48.

16. Harper PS. *Practical Genetic Counselling*, 5th Edition. Boston: Butterworth Heinemann Publishers, 1998: 197-9.

17. Sanders DD, Stephens TD. Review of drug-induced limb defects in mammals. *Teratology* 1991; 44: 335-54.

18. Miller T, Stromland K. Teratogen update: Thalidomide: A review, with a focus on ocular findings and new potential uses. *Teratology* 1999; 60: 306-21.

19. Reprotox: An Information System on Environmental Hazards to Human Reproduction and Development. Thalidomide, RTC 2487; Misoprostol, RTC 2396; Methotrexate, RTC 1036; Aminopterin, RTC 3076. Isotretinoin, RTC 1098. 2001. (Available: http://reprotox.org/).

20. Honein MA, Paulozzi LJ, Erickson JD. Continued occurrence of Accutane-exposed pregnancies. *Teratology* 2001; 64: 142-7.

21. Firth HV, Boyd PA, Chamberlain P, Mackenzie IZ, Lindenbaum RH, Huson SM. Severe limb abnormalities after chorionic villus sampling at 56-66 days' gestation. *Lancet* 1991; 337: 762-3.

22. Eurocat Central Registry, Belgium. Chorionic villus sampling and limb reduction. EUROCAT *Newsletter* 1992; 6(2).

23. Jahoda MGJ, Brandenburg H, Cohen-Overbeek T et al. Terminal transverse limb defects and early chorionic villus sampling: evaluation of 4300 cases with completed follow-up. *Am J Med Genet* 1993; 43: 483-5.

24. Olney RS et al. Letter to the Editor: Limb defects and gestational age at chorionic villus sampling. *Lancet* 1994; 344: 476.

25. Brambati B, Tului L. Prenatal genetic diagnosis through chorionic villus sampling. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: John Hopkins University Press, 1998: 168-72.

26. WHO/PAHO Consultation on CVS. Evaluation of Chorionic villus sampling safety. *Prenat Diagn* 1999; 19: 97-9.

27. Botto LD, Olney RS, Mastroiacovo P et al. Chorionic villus sampling and transverse digital deficiencies: evidence for anatomic and gestational-age specificity of the digital deficiencies in two studies. *Am J Med Genet* 1996; 62: 173-8.

28. Elias S, Simpson JL. Prenatal Diagnosis. Safety of Chorionic Villus Sampling. In: Rimoin DL, Connor JM, Pyeritz RE (Eds.), *Emery and Rimoin's Principles and Practice of Medical Genetics*, 3rd Edition. New York: Churchill Livingstone Publishing, 1996: 569-70.

29. Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Techniques of prenatal diagnosis. 2001. (Available: http://sogc.medical.org/SOGCnet/sogc_docs/common/guide/pdfs/ps105.pdf).

30. Reprotox: An Information System on Environmental Hazards to Human Reproduction and Development. Cigarette Smoking, RTC 1062. 2002. (Available: http://reprotox.org/dbtw-wpd/exec/dbtwpcgi.exe.).

31. Wasserman CR, Shaw GM, O'Malley CD et al. Parental cigarette smoking and risk for congenital anomalies of the heart, neural tube, or limb. *Teratology* 1996; 53: 261-7.

32. Kallen K. Maternal smoking during pregnancy and limb reduction malformations in Sweden. *Am J Pub Health* 1997; 87: 29-32.

33. Czeizel AE, Kodaf I, Lenz W. Smoking during pregnancy and congenital limb deficiency. *Br Med J* 1994; 308: 1473-7.

34. James A. Letter to the Editor: Marine pollution and limb reduction defects. *Lancet* 1994; 343: 990-1.

35. Wright MJ, Newell JN, Charlton ME et al. Limb reduction defects in the northern region of England 1985-1992. *J of Epidemiol and Com Health* 1995; 49: 305-8.

36. Shaw GM, O'Malley CD, Wasserman CR et al. Maternal periconceptional use of multivitamins and reduced risk for conotruncal heart and limb reduction defects among offspring. *Am J Med Genet* 1995; 59: 536-45.

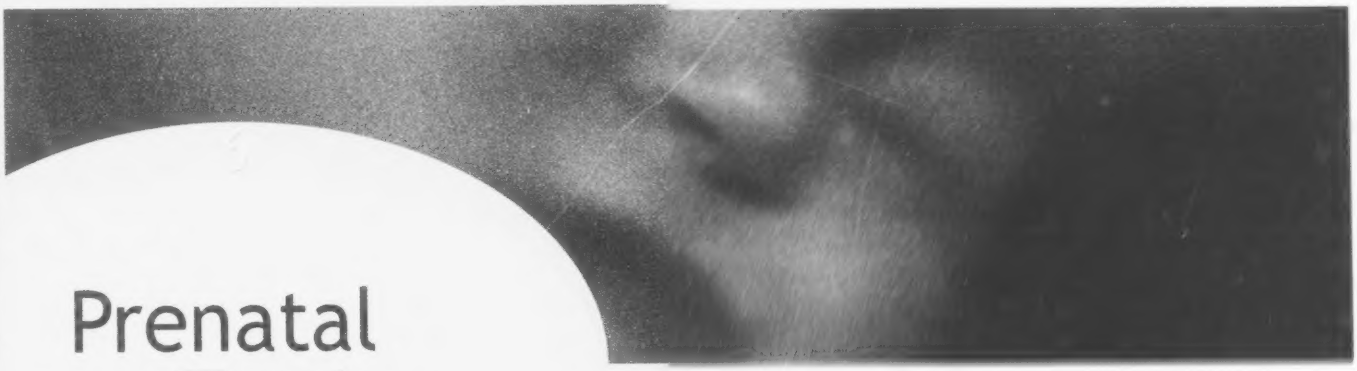
37. Werler MM, Hayes C, Louik C et al. Multivitamin supplementation and risk of birth defects. *Am J Epidemiol* 1999; 150: 675-82.

38. Shashi V, Rickheim A, Pettenati MJ. Maternal homozygosity for the common MTHFR mutation as a potential risk factor for offspring with limb defects. *Am J Med Genet* 2001; 100: 25-9.

39. Alberta Congenital Anomalies Surveillance System. *Fourth Report: 1980-1998*. Prepared by Lowry RB, Sibbald BS, Wang FL. Alberta Children's Hospital Research Centre, Alberta Health, Health Surveillance and the Division of Vital Statistics, Alberta Registries, 2001.

40. Castilla EE, Ashton-Prolla P, Barreda-Mejia E et al. Thalidomide, a current teratogen in South America. *Teratology* 1996; 54: 273-7.

41. Stoll C, Wiesel A, Queisser-Luft A et al. Evaluation of the prenatal diagnosis of limb reduction deformities. EUROSCAN Study Group. *Prenat Diagn* 2000; 20: 811-8.



Prenatal Testing

In the general population, 2%–3% of children are born with a serious congenital anomaly. The objective of prenatal testing is to provide reassurance to prospective parents early in pregnancy. The majority of couples receiving prenatal testing are provided with such reassurance, as serious congenital anomalies are found in less than 5% of pregnancies that undergo prenatal diagnosis.

Prenatal testing options offered to couples are categorized into procedures that either have screening or diagnostic capabilities in detecting congenital anomalies. Prenatal screening tests indicate if the pregnancy is at *increased risk* for a congenital anomaly, whereas diagnostic tests indicate whether the fetus is *affected* with the genetic anomaly.

Prenatal Screening

The validity of a screening test is measured by its ability to correctly categorize women who have an affected pregnancy as *test positive*, and those women without an affected pregnancy as *test negative*.[3] Screening tests are characterized by several terms presented below.

Preconception screening

All couples have a right to know if they are at increased risk of having a child with a congenital anomaly. The essential aim of preconception screening is to identify couples at increased risk over the background population risk for having a child with a congenital anomaly *before* a pregnancy is considered.

This screening approach allows couples to make an informed choice about proceeding with a pregnancy after they have been informed about their risks. Additionally, initiating or enhancing primary preventive strategies among couples identified as high risk may be indicated preconceptionally to improve the likelihood of a healthy outcome. Examples would include maintaining excellent glucose control in an insulin-dependent diabetic woman, changing anticonvulsant therapy in an epileptic woman, and ensuring folic acid supplementation among all women, particularly those with an increased risk for neural tube defects (NTDs). Preconception identification of couples who, by virtue of their ethnic background, are known or suspected carriers of certain genetic disorders enables further carrier testing and genetic counselling.

36-41

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

Micromedia
ProQuest

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

Prenatal screening test characteristics

	Congenital anomaly present	Congenital anomaly absent
Screen test positive	*True positive (TP)*	*False positive (FP)*
Screen test negative	*False negative (FN)*	*True negative (TN)*

Sensitivity: The probability of testing positive on a prenatal screening test if the congenital anomaly is present (TP/TP + FN). (Note: detection rate is an alternate term used by many of the referenced papers to signify the sensitivity of the test.)

Specificity: The probability of testing negative on a prenatal screening test if the congenital anomaly is absent (TN/TN + FP).

Positive predictive value: The probability that a congenital anomaly is present given that the prenatal screening test is positive. (TP/TP + FP)

Negative predictive value: The probability that a congenital anomaly is absent given that the prenatal screening test is negative (TN/TN + FN).

False negative rate: The proportion of pregnancies that will test negative given that the congenital anomaly is present.

False positive rate: The proportion of pregnancies that will test positive given that the congenital anomaly is absent.

Source: Table and definitions modified from Hennekens[3] and Last.[4]

Preconception genetic counselling provides couples with an understanding of all the implications of the congenital anomaly in question, the risks of occurrence or recurrence, and the prenatal testing choices available for their pregnancy. Preconception genetic counselling assists and supports couples in decision making about their reproductive choices.[2]

Maternal age screening

Prenatal screening began with the identification of advanced maternal age as a risk factor for Down syndrome (DS). It has been well established that advanced maternal age is correlated with an increasing risk for several chromosome abnormalities. In Canada and most other countries, women over 35 years of age at delivery are considered at increased risk for fetal chromosome problems and are routinely offered prenatal diagnosis (amniocentesis or chorionic villus sampling (CVS)). As 70% of infants with DS are born to women under 35 years of age, most cases go undetected with this screen.[5] Maternal age screening is accepted as a standard of care across Canada but it is under considerable scrutiny, particularly in view of the improved screening tests now available. This does not, however, preclude the important role prenatal care providers have in educating women of the risks associated with advancing maternal age.

Maternal serum screening

Remarkable advances in prenatal screening have taken place since the first observation in 1973 of elevated maternal serum alpha-fetoprotein (MSAFP) with anencephaly. The detection rate (sensitivity) for open NTDs with MSAFP screening at 16 to 18 weeks in pregnancy is approximately 85% for open spina bifida and 95% for anencephaly, with a false positive rate of 2%.[6]

Preconception screening identifies couples at increased risk for having a child with a congenital anomaly prior to conception. Risk factors that may be identified through preconception screening and counselling include:

- advanced maternal age
- a previous child with a congenital anomaly
- a family history of genetic concern
- a person has, or is suspected of having, a particular genetic condition
- a maternal disease associated with an adverse pregnancy outcome
- couples at increased risk for specific genetic conditions based on their ethnicity
- an environmental, occupational exposure including medications, infectious agents, etc.

The measure of additional maternal serum fetal-placental proteins has enabled maternal serum screening (MSS) to expand its role as a screen for two types of chromosome problems, DS and trisomy 18. This multianalyte serum screen, also known as the triple screen, measures the concentration of fetal-placental proteins in the maternal circulation, namely MSAFP, unconjugated estriol (E3) and human chorionic gonadotropin (hCG). At 15 to 16 weeks in pregnancy, the median values of these serum proteins, or analytes, are sufficiently different from normal range in fetuses with DS and trisomy 18. Taking into account the woman's age-related risk and the serum results, a woman is assigned a modified risk of having a DS-affected or trisomy 18-affected pregnancy. Women are subsequently offered prenatal diagnosis (amniocentesis) if their risk of an affected pregnancy is higher than the procedure-related miscarriage risk associated with amniocentesis.

This method of screening for fetal chromosome problems is more effective than maternal age alone. For this reason, many women of advanced maternal age select MSS prior to proceeding with a decision regarding amniocentesis. The reported sensitivity of MSS for DS and trisomy 18 is dependent upon maternal age but is approximately 60%-70%.[7] One drawback to this screen is the relatively high number of women who receive a false positive screen result. Depending on maternal age and the screen cut-off, approximately 1 in 10 to 1 in 20 women who undergo testing will receive "an increased risk" test result. Of these women, only 1%-2% will have a pregnancy affected with DS, trisomy 18 or an NTD. However, many of these women will proceed with amniocentesis and place their pregnancies at increased risk for miscarriage. Several centres across the world continue to investigate additional serum markers aimed at increasing the validity (increasing the sensitivity without decreasing the specificity) of second trimester MSS. Screening for markers found in maternal urine is also being introduced in selected centres.

Availability of MSS testing

Maternal serum screening is endorsed by the Canadian Task Force on Preventive Health Care (formerly the Canadian Task Force on the Periodic Health Examination) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) with the provision that the screen is offered within a comprehensive prenatal screening and diagnosis program, including patient education and follow-up counselling.[8,9] The availability of MSS in Canada and in many other countries is dependent upon region-specific initiatives and available resources.

First trimester screening

Maternal anxiety provoked by false positive screen results and the increased utilization of invasive prenatal diagnostic tests later in the pregnancy are two major drawbacks to second trimester MSS. Research is placing more emphasis on valid screening tests that could be offered earlier in pregnancy.

Prenatal screening test characteristics

	Congenital anomaly present	Congenital anomaly absent
Screen test positive	True positive (TP)	False positive (FP)
Screen test negative	False negative (FN)	True negative (TN)

Sensitivity: The probability of testing positive on a prenatal screening test if the congenital anomaly is present (TP/TP + FN). (Note: detection rate is an alternate term used by many of the referenced papers to signify the sensitivity of the test.)

Specificity: The probability of testing negative on a prenatal screening test if the congenital anomaly is absent (TN/TN + FP).

Positive predictive value: The probability that a congenital anomaly is present given that the prenatal screening test is positive. (TP/TP + FP)

Negative predictive value: The probability that a congenital anomaly is absent given that the prenatal screening test is negative (TN/TN + FN).

False negative rate: The proportion of pregnancies that will test negative given that the congenital anomaly is present.

False positive rate: The proportion of pregnancies that will test positive given that the congenital anomaly is absent.

Source: Table and definitions modified from Hennekens[3] and Last.[4]

Preconception genetic counselling provides couples with an understanding of all the implications of the congenital anomaly in question, the risks of occurrence or recurrence, and the prenatal testing choices available for their pregnancy. Preconception genetic counselling assists and supports couples in decision making about their reproductive choices.[2]

Maternal age screening

Prenatal screening began with the identification of advanced maternal age as a risk factor for Down syndrome (DS). It has been well established that advanced maternal age is correlated with an increasing risk for several chromosome abnormalities. In Canada and most other countries, women over 35 years of age at delivery are considered at increased risk for fetal chromosome problems and are routinely offered prenatal diagnosis (amniocentesis or chorionic villus sampling (CVS)). As 70% of infants with DS are born to women under 35 years of age, most cases go undetected with this screen.[5] Maternal age screening is accepted as a standard of care across Canada but it is under considerable scrutiny, particularly in view of the improved screening tests now available. This does not, however, preclude the important role prenatal care providers have in educating women of the risks associated with advancing maternal age.

Maternal serum screening

Remarkable advances in prenatal screening have taken place since the first observation in 1973 of elevated maternal serum alpha-fetoprotein (MSAFP) with anencephaly. The detection rate (sensitivity) for open NTDs with MSAFP screening at 16 to 18 weeks in pregnancy is approximately 85% for open spina bifida and 95% for anencephaly, with a false positive rate of 2%.[6]

Preconception screening identifies couples at increased risk for having a child with a congenital anomaly prior to conception. Risk factors that may be identified through preconception screening and counselling include:

- advanced maternal age
- a previous child with a congenital anomaly
- a family history of genetic concern
- a person has, or is suspected of having, a particular genetic condition
- a maternal disease associated with an adverse pregnancy outcome
- couples at increased risk for specific genetic conditions based on their ethnicity
- an environmental, occupational exposure including medications, infectious agents, etc.

The measure of additional maternal serum fetal-placental proteins has enabled maternal serum screening (MSS) to expand its role as a screen for two types of chromosome problems, DS and trisomy 18. This multianalyte serum screen, also known as the triple screen, measures the concentration of fetal-placental proteins in the maternal circulation, namely MSAFP, unconjugated estriol (E3) and human chorionic gonadotropin (hCG). At 15 to 16 weeks in pregnancy, the median values of these serum proteins, or analytes, are sufficiently different from normal range in fetuses with DS and trisomy 18. Taking into account the woman's age-related risk and the serum results, a woman is assigned a modified risk of having a DS-affected or trisomy 18-affected pregnancy. Women are subsequently offered prenatal diagnosis (amniocentesis) if their risk of an affected pregnancy is higher than the procedure-related miscarriage risk associated with amniocentesis. This method of screening for fetal chromosome problems is more effective than maternal age alone. For this reason, many women of advanced maternal age select MSS prior to proceeding with a decision regarding amniocentesis. The reported sensitivity of MSS for DS and trisomy 18 is dependent upon maternal age but is approximately 60%-70%.[7] One drawback to this screen is the relatively high number of women who receive a false positive screen result. Depending on maternal age and the screen cut-off, approximately 1 in 10 to 1 in 20 women who undergo testing will receive "an increased risk" test result. Of these women, only 1%-2% will have a pregnancy affected with DS, trisomy 18 or an NTD. However, many of these women will proceed with amniocentesis and place their pregnancies at increased risk for miscarriage. Several centres across the world continue to investigate additional serum markers aimed at increasing the validity (increasing the sensitivity without decreasing the specificity) of second trimester MSS. Screening for markers found in maternal urine is also being introduced in selected centres.

Availability of MSS testing

Maternal serum screening is endorsed by the Canadian Task Force on Preventive Health Care (formerly the Canadian Task Force on the Periodic Health Examination) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) with the provision that the screen is offered within a comprehensive prenatal screening and diagnosis program, including patient education and follow-up counselling.[8,9] The availability of MSS in Canada and in many other countries is dependent upon region-specific initiatives and available resources.

First trimester screening

Maternal anxiety provoked by false positive screen results and the increased utilization of invasive prenatal diagnostic tests later in the pregnancy are two major drawbacks to second trimester MSS. Research is placing more emphasis on valid screening tests that could be offered earlier in pregnancy.

One example is the measurement of two maternal serum analytes, hCG and pregnancy associated plasma protein-A (PAPP-A) at 10 to 14 weeks in pregnancy.[5,10] Depending upon the selected cut-off for a positive screen result, the sensitivity is reportedly similar to second trimester MSS. Then, depending on the regional practice guidelines, the option of prenatal diagnosis using CVS or early amniocentesis, could be offered as early as 11 to 12 weeks in pregnancy. First trimester serum screening, however, is not routinely offered in Canada.

The use of ultrasound screening for fetal chromosome problems in the first trimester is at the forefront in prenatal testing research and clinical practice. First trimester ultrasound screening tests are offered in a limited number of centres in Canada as either nuchal translucency (NT) screening alone or as part of an integrated prenatal screening (IPS) program.

First trimester NT screening

In the 1990s, screening by a combination of maternal age and NT at 10 to 14 weeks in pregnancy was introduced. This ultrasound test utilizes the measurement of the thickness of the skin fold behind the fetal neck. An NT measurement above the expected median for a given gestational age increases the risk for a number of chromosome problems, more specifically DS, as well as congenital heart defects (CHDs). The larger the NT measurement, the higher the modified risk and, inversely, the smaller the NT measure, the lower the risk. A modified risk is calculated using maternal age, gestational age and the degree of deviation in NT thickness measurement from the median. The detection rate (sensitivity) and false positive rate for DS vary between 40%-70% and 2%-7%, respectively, depending upon factors such as fetal positioning and the expertise of the ultrasound technician.[11] A multicentre study of 96,000 pregnancies screened in 22 centres by 306 sonographers reported a sensitivity and false positive rate for DS of 82% and 8.3%, respectively.[12,13]

Availability of NT screening

Nuchal translucency certification is considered a requirement to obtain reliable measurements. Nuchal translucency training and certification is offered through the Fetal Medicine Foundation (FMF) in London, England, and a number of satellite programs throughout the world. In Britain alone, there are approximately 28 centres carrying out NT screening. Several Canadian radiologists and perinatologists have received NT screening certification, and NT screening is offered on a limited basis in Canada.

Integrated prenatal screening

Integrated prenatal screening combines maternal age and NT screening with first and second trimester maternal serum analytes as a non-invasive screen for DS. Integrated prenatal screening may detect 80%-90% of DS cases with a false positive rate of 0.9%.[14,15] This approach to screening utilizes first trimester (11 to 14 weeks) NT screening and serum marker measurements of PAPP-A, followed by second trimester (15 to 17 weeks) serum screening using the triple markers, AFP, E3 and hCG. Women participating in IPS receive one final screen result following the second stage of testing. In Canada, Ontario has offered IPS as a clinical research project since 1999. The final results of the Ontario pilot initiative are pending.

Second trimester ultrasound screening

The use of prenatal ultrasound has developed over the past two decades. Second trimester ultrasound has both screening and diagnostic capabilities.[16] As a screening tool, second trimester ultrasound can detect subtle signs suggestive of a fetal congenital anomaly. In the case of a suspected fetal chromosome problem, confirmatory testing such as amniocentesis is usually offered to provide a final diagnosis of the congenital anomaly. As a diagnostic tool, second trimester ultrasound can diagnose obvious anomalies, such as anencephaly. In these cases, pregnancy management decisions are often made without further testing.

Second trimester ultrasound testing is considered a routine standard of care in Canada.[17] There is considerable variation in the reported detection rates of fetal anomalies before 24 weeks in low-risk populations. Studies have demonstrated a low sensitivity, varying from 17%-35%, but a high specificity of 99%.[18-21] When targeting high-risk populations, the sensitivity of ultrasound screening for congenital anomalies is reported to be greater than 90%.[19]

Most fetuses with major chromosome abnormalities such as trisomy 18, 13 and 21 have either external or internal abnormalities that can be recognized by detailed second trimester ultrasound screening.[16] Minor ultrasound "markers," including echogenic bowel, choroid plexus cysts and echogenic intracardiac focus, are transient physiologic sonographic findings associated with an increased risk for chromosome abnormalities. In some settings, these markers, combined with maternal age, have been used to modify the risk for DS and other chromosome abnormalities.[22] The accuracy of this approach remains controversial.

As a result of the improved capabilities of ultrasound and MSS, there has been a considerable shift in the indications for invasive prenatal diagnosis. Increasingly, amniocentesis is offered to women previously considered to be low risk, based on MSS test results or the outcome of their 18-week ultrasound.

Prenatal Diagnosis

Amniocentesis, CVS and cordocentesis (also referred to as percutaneous umbilical blood sampling) are invasive prenatal tests used to diagnose fetal chromosome abnormalities (Table 6.1). Chromosome analysis of fetal cells is performed by means of routine karyotyping. Fluorescent in-situ hybridization of uncultured fetal cells is a rapid reliable test offered as an adjunct to routine karyotyping in certain high-risk circumstances where significant abnormal ultrasound findings are identified and obstetric management is dependent on rapid determination of fetal aneuploidy.

Amniocentesis is the most commonly performed procedure, conventionally offered at 15 to 16 weeks in pregnancy. The procedure-related miscarriage rate at this gestation is 0.5%-1.0%.[23-28] A major limitation to amniocentesis has been the late timing of the procedure. In cases in which a chromosome problem is diagnosed, the women are then faced with a major decision — to either continue or end the pregnancy. Unfortunately, early amniocentesis (performed prior to 13 weeks in pregnancy) has been shown to carry increased risks for pregnancy loss and talipes equinovarus (club foot).[25,27-29]

Chorionic villus sampling became widely available by the early 1980s and is the procedure most commonly used in the first trimester for fetal karyotyping and molecular prenatal diagnosis. The procedure-related miscarriage risk has been reported to be higher than for mid-trimester amniocentesis.[8] However, comparisons between CVS and mid-trimester amniocentesis pregnancy loss rates are confounded by non-viable fetuses that are spontaneously aborted prior to 15 weeks. An evaluation of 216,381 CVS cases reported through the World Health Organization (WHO)-sponsored CVS Registry suggested a procedure-related pregnancy loss rate comparable to that of second trimester amniocentesis.[30] The WHO CVS Registry also evaluated the temporal relation between CVS and limb reduction defects (LRDs) and did not support an increased risk among the registry cases with CVS performed at or greater than eight weeks in pregnancy.[30,31] Chorionic villus sampling is usually performed between 10 to 12 weeks in pregnancy in Canada[8] and the United States.[26]

Cordocentesis is a test reserved for high-risk pregnancies and carries an approximate 3% risk for pregnancy loss.[23] This procedure is often considered when amniocentesis may not be achievable (as in the case of severe oligohydramnios), significant abnormal ultrasound findings are identified later in pregnancy and obstetric management is dependent on a rapid chromosome diagnosis.

Table 6.1

Summary of prenatal diagnostic tests available in Canada

	Chorionic villus sampling (CVS)	Amniocentesis	Cordocentesis
Purpose	Primarily performed to obtain a *fetal karyotype*; to diagnose or rule out fetal chromosome problems. Can also be used for DNA testing if indicated.		
Tissue sampled	Tissue destined to become placenta	Amniotic fluid	Fetal blood
Timing	11-13 weeks	Routinely offered ≥ 15 weeks	Later in second trimester (usually > 16 weeks)
Risk of miscarriage related to the procedure	1%-2% transabdominal procedure 2%-6% transcervical procedure	0.5%-1.0% for a procedure performed at 15-16 weeks' gestation	~ 3%
Additional procedure-related risks	Risk of LRDs has been reported to be slightly increased over the baseline risk when performed prior to 8 weeks' gestation	2%-3% risk of premature rupture of membranes, transient spotting, cramping Risk of club foot increased over the baseline risk in procedures performed ≤ 12 weeks' gestation	Fetal bradycardia Fetal bleeding
Accuracy of chromosome results	Highly accurate 1%-2% of results are difficult to interpret due to *confined placental mosaicism**	Highly accurate	Highly accurate
Advantage of the test	Performed early in pregnancy with results available by 14-15 weeks CVS is preferred for molecular DNA testing	Fluid also tested for alpha-fetoprotein (NTD screening) Lower risk of procedure-related miscarriage	Reserved for high-risk pregnancies where a rapid diagnosis is required for pregnancy management

Adapted from: Society of Obstetricians and Gynaecologists of Canada, 2001.[8]

*Confined placental mosaicism: a proportion of cells identified as having a normal complement of 46 chromosomes, believed to be derived from the fetus, and the remaining cells having a chromosome abnormality, believed to be derived from placental tissue.

The Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists and the Genetics Committee of the SOGC regularly publish prenatal diagnosis guidelines that are considered the standard of care across the country.[8] In general terms, prenatal diagnosis for the detection of fetal chromosome problems is offered to women when the estimated risk of delivering a child with a chromosome abnormality is greater than or equal to the procedure-related miscarriage risk. Advanced maternal age, "positive" MSS and the identification of an ultrasound marker associated with fetal chromosome problems are the most common indications for prenatal diagnosis.

Additional prenatal diagnostic tests are not readily available. Isolation of fetal cells from maternal circulation in the early first trimester to test for genetic anomalies is a non-invasive diagnostic approach with the potential to revolutionize prenatal testing, but is still in the early research phase. Preimplantation genetic diagnosis (PGD) is a method used to analyze chromosomes or DNA of a single cell (blastocyst) during the earliest stages of human development, before implantation. This method requires assisted reproductive technologies and is reserved for pregnancies at high risk for inherited single gene defects and chromosome anomalies.[32] Presently, PGD is not routinely available in Canada.

Impact of Prenatal Diagnosis on Birth Prevalence of Congenital Anomalies

The impact of prenatal diagnosis on the birth prevalence of serious congenital anomalies depends upon several variables, including access to and utilization of prenatal testing, as well as the availability of and attitudes towards pregnancy termination following a prenatal diagnosis of an anomaly. A recent international report highlighted the dramatic impact of prenatal diagnosis on the birth prevalence of NTDs (Table 6.2).

Table 6.2

Proportion of terminations of pregnancy (TOP) among total number of neural tube defect (NTD) cases recorded, by country/registry, *1997-1998*

Country/registry	Number of births	Neural tube defects*			
		Live births and stillbirths (N)	TOP (N)	Total (N)	Proportion of TOP (%)
Atlanta, USA	88,528	46	32	82	39.0
England and Wales	1,284,096	160	542	702	77.2
Finland	116,911	50	60	110	54.5
France	306,465	35	163	198	82.3
Hungary	198,791	43	67	110	60.9
Israel	39,963	6	1	7	14.3
Italy	305,894	66	105	171	61.4
Northern Netherlands	39,338	19	9	28	32.1
Norway	118,640	51	26	77	33.8

Source: Goujard, 2001.[33]

*Anencephaly and spina bifida.

N – number of cases.

TOP – terminations of pregnancy.

Table 6.1

Summary of prenatal diagnostic tests available in Canada

	Chorionic villus sampling (CVS)	**Amniocentesis**	**Cordocentesis**
Purpose	Primarily performed to obtain a *fetal karyotype*: to diagnose or rule out fetal chromosome problems. Can also be used for DNA testing if indicated.		
Tissue sampled	Tissue destined to become placenta	Amniotic fluid	Fetal blood
Timing	11-13 weeks	Routinely offered > 15 weeks	Later in second trimester (usually > 16 weeks)
Risk of miscarriage related to the procedure	1%-2% transabdominal procedure 2%-6% transcervical procedure	0.5%-1.0% for a procedure performed at 15-16 weeks' gestation	~ 3%
Additional procedure-related risks	Risk of LRDs has been reported to be slightly increased over the baseline risk when performed prior to 8 weeks' gestation	2%-3% risk of premature rupture of membranes, transient spotting, cramping Risk of club foot increased over the baseline risk in procedures performed ≤ 12 weeks' gestation	Fetal bradycardia Fetal bleeding
Accuracy of chromosome results	Highly accurate 1%-2% of results are difficult to interpret due to *confined placental mosaicism**	Highly accurate	Highly accurate
Advantage of the test	Performed early in pregnancy with results available by 14-15 weeks CVS is preferred for molecular DNA testing	Fluid also tested for alpha-fetoprotein (NTD screening) Lower risk of procedure-related miscarriage	Reserved for high-risk pregnancies where a rapid diagnosis is required for pregnancy management

Adapted from: Society of Obstetricians and Gynaecologists of Canada, 2001.[1]

*Confined placental mosaicism: a proportion of cells identified as having a normal complement of 46 chromosomes, believed to be derived from the fetus, and the remaining cells having a chromosome abnormality, believed to be derived from placental tissue.

The Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists and the Genetics Committee of the SOGC regularly publish prenatal diagnosis guidelines that are considered the standard of care across the country.[7] In general terms, prenatal diagnosis for the detection of fetal chromosome problems is offered to women when the estimated risk of delivering a child with a chromosome abnormality is greater than or equal to the procedure-related miscarriage risk. Advanced maternal age, "positive" MSS and the identification of an ultrasound marker associated with fetal chromosome problems are the most common indications for prenatal diagnosis.

Additional prenatal diagnostic tests are not readily available. Isolation of fetal cells from maternal circulation in the early first trimester to test for genetic anomalies is a non-invasive diagnostic approach with the potential to revolutionize prenatal testing, but is still in the early research phase. Preimplantation genetic diagnosis (PGD) is a method used to analyze chromosomes or DNA of a single cell (blastocyst) during the earliest stages of human development, before implantation. This method requires assisted reproductive technologies and is reserved for pregnancies at high risk for inherited single gene defects and chromosome anomalies.[12] Presently, PGD is not routinely available in Canada.

Impact of Prenatal Diagnosis on Birth Prevalence of Congenital Anomalies

The impact of prenatal diagnosis on the birth prevalence of serious congenital anomalies depends upon several variables, including access to and utilization of prenatal testing, as well as the availability of and attitudes towards pregnancy termination following a prenatal diagnosis of an anomaly. A recent international report highlighted the dramatic impact of prenatal diagnosis on the birth prevalence of NTDs (Table 6.2).

Table 6.2

Proportion of terminations of pregnancy (TOP) among total number of neural tube defect (NTD) cases recorded, by country/registry, 1997-1998

Country/registry	Number of births	Neural tube defects*			
		Live births and stillbirths (N)	TOP (N)	Total (N)	Proportion of TOP (%)
Atlanta, USA	88,528	46	32	82	39.0
England and Wales	1,284,096	160	542	702	77.2
Finland	116,911	50	60	110	54.5
France	306,465	35	163	198	82.3
Hungary	198,791	43	67	110	60.9
Israel	39,963	6	1	7	14.3
Italy	305,894	66	105	171	61.4
Northern Netherlands	39,338	19	9	28	32.1
Norway	118,640	51	26	77	33.8

Source: Goujard, 2001.
*Anencephaly and spina bifida.
N = number of cases.
TOP = terminations of pregnancy.

The Prenatal Diagnosis Committee of the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) has been monitoring the impact of prenatal diagnosis on the prevalence of DS since 1993.[34] In 1999, 14 programs provided data on 1,757 cases. As a proportion of all recorded cases affected with DS, 53.2% were prenatally diagnosed and electively terminated. The rate of pregnancy termination of DS cases ranged from 26.7% in Alberta, Canada, to 84% in Paris, France. The prevalence at birth of DS decreased over seven years in many programs that showed the highest rates of terminations, suggesting that a high proportion of prenatally diagnosed cases were terminated.

Report on Prenatal Testing Practices in Canada

Surveillance of prenatal testing practices in provinces and territories will be an ongoing and vital component of the accurate surveillance of congenital anomalies in Canada. Access to and utilization of prenatal testing services varies considerably among the provinces and territories. These practices have an impact on the birth prevalence of many congenital anomalies. To explore this important area further, the Division of Health Surveillance and Epidemiology in the Centre for Healthy Human Development at Health Canada, in collaboration with the Canadian College of Medical Geneticists, has undertaken a national prenatal testing survey. The objective of this survey is to outline what prenatal testing services are available within the provinces and territories and how this may relate to the regional birth prevalence of congenital anomalies. Genetic centres and cytogenetic laboratories across the country have been contacted to provide information with regard to the types of prenatal genetic testing they offer and the way in which their services are utilized. The final report of this prenatal testing survey will soon be available through Health Canada.

References

1. Harper PS. *Practical Genetic Counselling*, 5th Edition. Boston: Butterworth Heinemann, 1998: 9-13.
2. Milunsky A, Milunsky J. Genetic counseling: Preconception, prenatal and perinatal. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 1-3.
3. Hennekens CH, Buring J. Statistical Association. In: Mayrent SL (Ed.), *Epidemiology in Medicine*. Toronto: Little, Brown and Company, 1987: 331-333.
4. Last JM. *Dictionary of Epidemiology*, 2nd Edition. New York: Oxford University Press. 1988.
5. Wald NJ, Smith GL, Denesen JW, Petterson K. Serum screening for Down's syndrome between 8 and 14 weeks of pregnancy. *Br J Obstet Gynecol* 1996; 103: 407-12.
6. Milunsky A. Maternal serum screening for neural tube and other defects. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 635-701.
7. Milunsky A. Multianalyte maternal serum screening for chromosome defects. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 702-49.
8. Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Techniques of prenatal diagnosis. 2001. (Available: http://sogc.medical.org/SOGCnet/sogc_docs/common/guide/pdfs/ps105.pdf).

9. Dick PT, with the Canadian Task Force on the Periodic Health Examination. Periodic Health Examination, 1996 update: 1. Prenatal screening for and diagnosis of Down syndrome. *CMAJ* 1996; 154: 465-77.

10. Casals E, Fortuny A, Grudzinskas JG et al. First trimester biochemical screening for Down syndrome with the use of PAPP-A, AFP and B-hCG. *Prenat Diagn* 1996; 16: 405-10.

11. Chitty LS, Pandya P. Ultrasound screening for fetal abnormalities in the first trimester. *Prenat Diagn* 1997; 17: 1269-82.

12. Haddow JE. Commentary. Antenatal screening for Down syndrome: where are we and where next? *Lancet* 1998; 352: 336-7.

13. Snijders RJM, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10-14 weeks of gestation. *Lancet* 1998; 352: 343-6.

14. Wald NJ, Watt HC, Hackshaw AK. Integrated screening for Down's syndrome on the basis of tests performed in the first and second trimesters. *N Engl J Med* 1999; 341: 461-7.

15. Wald NJ, Hackshaw AK. Combining ultrasound and biochemistry in first-trimester screening for Down syndrome. *Prenat Diagn* 1997; 17: 821-9.

16. Callen PW. The obstetric ultrasound examination. In: Callen PW (Ed.), *Ultrasonography in Obstetrics and Gynecology*, 4th Edition. New York: W.B. Saunders Company, 2000: 1-5, 12-14.

17. Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Guidelines for ultrasound as part of routine prenatal care. *SOGC Journal* 1999; August: 78. (Available: http://sogc.medical.org/SOGCnet/sogc_ ocs/common/guide/pdfs/ps78.pdf).

18. Anderson N, Boswell O, Duff G. Prenatal sonography for the detection of fetal anomalies. Results of a prospective study and comparison with prior series. *Am J Roentgenol* 1995; 165: 943.

19. Villes YG, Nicolaides KH, Campbell S. Prenatal diagnosis of fetal malformations by ultrasound. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 750-812.

20. Pilu F, Falco P, Perolo A, Visentin A. Ultrasound evaluation of the fetal neural axis. In: Callen PW (Ed.), *Ultrasonography in Obstetrics and Gynecology*, 4th Edition. New York: W.B. Saunders Company, 2000: 277-306.

21. Stoll C, Garne E, Clementi M and EUROSCAN Study Group. Evaluation of prenatal diagnosis of associated congenital heart diseases by fetal ultrasonographic examination in Europe. *Prenat Diagn* 2001; 21: 243-52.

22. Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome. A meta-analysis. *JAMA* 2001; 285: 1044-55.

23. Elias S, Simpson JL, Bombard AT. Amniocentesis and fetal blood sampling. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 53-82.

24. Tabor A, Madsen M, Obel EB et al. Randomized controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet* 1986; 8493: 1287-93.

25. Roper EC, Konje JC, De Chazal RC et al. Genetic amniocentesis: gestation-specific pregnancy outcome and comparison of outcome following early and traditional amniocentesis. *Prenat Diagn* 1999; 19: 803-7.

26. *Mortality and Morbidity Weekly Report (MMWR). Recommendations and Reports.* Chorionic villus sampling and amniocentesis: recommendations for prenatal counseling. 1995. (Available: www.cdc.gov/mmwr/preview/mmwrhtml/00038393.html).

27. Canadian Early and Mid-Trimester Amniocentesis Trial (CEMAT) Group. Randomised trial to assess safety and fetal outcome of early and midtrimester amniocentesis. *Lancet* 1998; 351: 242-7.

28. Wilson RD. Amniocentesis and chorionic villus sampling. *Curr Opin Obstet Gynecol* 2000; 12: 81-6.

29. Yoon G, Chernos J, Sibbald B et al. Association between congenital foot anomalies and gestational age at amniocentesis. *Prenat Diagn* 2001; 21: 1437-41.

30. WHO/PAHO Consultation on CVS. Evaluation of Chorionic villus sampling safety. *Prenat Diagn* 1999; 19: 97-9.

31. Brambati B, Tului L. Prenatal genetic diagnosis through chorionic villus sampling. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: John Hopkins University Press, 1998: 168-72.

32. Reproductive Genetics Institute. *History of International Working Group on Preimplantation Genetics*, 2001. (Available: www.reproductivegenetics.com/history.shtml).

33. Goujard J. *Comparison of Changes in Neural Tube Defects (NTDs) Prevalence in Relation to Primary Prevention Strategies: Public Health Policy-Making and Implementation. Final Report*. 2001: 17.

34. International Clearinghouse for Birth Defects Monitoring Systems. *Annual Report*. Rome, Italy, 2001.

Bibliography

Alberta Congenital Anomalies Surveillance System. *Fourth Report: 1980-1998*. Prepared by Lowry RB, Sibbald BS, Wang FL. Alberta Children's Hospital Research Centre, Alberta Health, Health Surveillance and the Division of Vital Statistics, Alberta Registries, 2001.

Allan LD, Cook A, Sullivan I, Sharland GK. Hypoplastic left heart syndrome: effects of fetal echocardiography on birth prevalence. *Lancet* 1991; 337: 959-61.

Anderson N, Boswell O, Duff G. Prenatal sonography for the detection of fetal anomalies. Results of a prospective study and comparison with prior series. *Am J Roentgenol* 1995; 165: 943.

Babock C. The fetal face and neck. In: Callen PW (Ed.), *Ultrasonography in Obstetrics and Gynecology*, 4th Edition. New York: W.B. Saunders Company, 2000: 307-27.

Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics* 1990; 85: 1-9.

Benn P, Egan JFX. Letters to the Editor: Survival of Down syndrome in utero. *Prenat Diagn* 2000: 20: 432-3.

Bianchi DW, Crombleholme TM, D'Alton ME. Myelomeningocele. In: *Fetology: Diagnosis and Management of the fetal patient*. Toronto: McGraw-Hill Medical Publishing Division, 2000: 159-71.

Bianchi DW, Crombleholme TM, D'Alton ME. Prenatal Imaging. In: *Fetology: Diagnosis and Management of the fetal patient*. Toronto: McGraw-Hill Medical Publishing Division, 2000: 6-9.

Bonin MM, Bretzlaff JA, Therrien MA, Trowe BH. Knowledge of periconceptional folic acid for the prevention of neural tube defects. *Arch Fam Med* 1998; 7: 438-42.

Borman B, Cryer C. Fallacies of international and national comparisons of disease occurrence in the epidemiology of neural tube defects. *Teratology* 1990; 42: 405-12.

Botto LD, Khoury MJ, Mulinare J, Erickson JD. Periconceptional multivitamin use and the occurrence of conotruncal heart defects: results from a population-based, case-control study. *Pediatrics* 1996; 98: 911-7.

Botto LD, Loffredo C, Scanlon KS et al. Vitamin A and cardiac outflow tract defects. *Epidemiology* 2001; 12: 491-6.

Botto LD, Lynberg MC, Erickson JD. Congenital heart defects, maternal febrile illness, and multivitamin use: a population-based study. *Epidemiology* 2001; 12: 485-90.

Botto LD, Mulinare J. Methylenetetrahydrofolate reductase gene and neural tube defects. *Am J Epidemiol* 1999; 150: 323-42.

Botto LD, Olney RS, Mastroiacovo P et al. Chorionic villus sampling and transverse digital deficiencies: evidence for anatomic and gestational-age specificity of the digital deficiencies in two studies. *Am J Med Genet* 1996; 62: 173-8.

Bower C, Stanley FJ. Dietary folate as a risk factor for neural tube defects: evidence from a case-control study in Western Australia. *Med J Aust* 1989; 150: 613-9.

Boyd PA, Wellesley DG, De Walle HEK et al. Evaluation of the prenatal diagnosis of neural tube defects by fetal ultrasonographic examination in different centres across Europe. *J Med Screen* 2000; 7: 169-74.

Brackley KJ, Kilby MD, Wright JG et al. Outcome after prenatal diagnosis of hypoplastic left heart syndrome: a case series. *Lancet* 2000; 356: 1143-7.

Brambati B, Tului L. Prenatal genetic diagnosis through chorionic villus sampling. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis. Prevention and Treatment*, 4th Edition. Baltimore: John Hopkins University Press, 1998: 168-72.

California Birth Defects Monitoring Program. *Information on heart defects*. 2002. (Available: www.cbdmp.org/).

Callen PW. The obstetric ultrasound examination. In: Callen PW (Ed.), *Ultrasonography in Obstetrics and Gynecology*, 4th Edition. New York: W.B. Saunders Company, 2000: 1-5, 12-14.

Callif-Daley FA, Huether CA, Edmonds LD. Evaluating false positives in two hospital discharge data sets of the birth defects monitoring program. *Public Health Rep* 1995; 110: 154-60.

Canadian Centre on Substance Abuse. *Joint Statement: Prevention of Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE) in Canada*. 1996. (Available: www.ccsa.ca/fasis/fassmnt.htm).

Canadian Early and Mid-Trimester Amniocentesis Trial (CEMAT) Group. Randomised trial to assess safety and fetal outcome of early and midtrimester amniocentesis. *Lancet* 1998; 351: 242-7.

Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. *Am J Med Genet* 1999; 3: 242-4.

Casals E, Fortuny A, Grudzinskas JG et al. First trimester biochemical screening for Down syndrome with the use of PAPP-A, AFP and B-hCG. *Prenat Diagn* 1996; 16: 405-10.

Castilla EE, Ashton-Prolla P, Barreda-Mejia E et al. Thalidomide, a current teratogen in South America. *Teratology* 1996; 54: 273-7.

Chitty LS, Pandya P. Ultrasound screening for fetal abnormalities in the first trimester. *Prenat Diagn* 1997; 17: 1269-82.

Christian MS, Brent RL. Teratogen update: evaluation of the reproductive and developmental risks of caffeine. *Teratology* 2001; 64: 51-78.

Cohen MM, Gorlin RJ, Fraser FC. Craniofacial Disorders. In: Emery A, Rimoin D (Eds.), *Principles and Practice of Medical Genetics*, 3rd Edition. New York: Churchill Livingstone, 1997: 1121-47.

Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. *Am J Med Genet* 1996; 62: 179-83.

Czeizel AE, Dudas E. Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992; 327: 1832-5.

Czeizel AE, Kodaf I, Lenz W. Smoking during pregnancy and congenital limb deficiency. *Br Med J* 1994; 308: 1473-7.

Dick PT, with the Canadian Task Force on the Periodic Health Examination. Periodic Health Examination, 1996 update: 1. Prenatal screening for and diagnosis of Down syndrome. *CMAJ* 1996; 154: 465-77.

Dodds L, King WD. Relation between trihalomethane compounds and birth defects. *Occup Environ Med* 2001; 7: 443-6.

Drug Therapy and Hazardous Substances Committee, Canadian Paediatric Society. Periconceptional use of folic acid for reduction of the risk of neural tube defects. *Paediatrics and Child Health* 1997; 2: 152-4.

Elias S, Simpson JL, Bombard AT. Amniocentesis and fetal blood sampling. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 53-82.

Elias S, Simpson JL. Prenatal Diagnosis. Safety of Chorionic Villus Sampling. In: Rimoin DL, Connor JM, Pyeritz RE (Eds.), *Emery and Rimoin's Principles and Practice of Medical Genetics*, 3rd Edition. New York: Churchill Livingstone Publishing, 1996: 569-70.

Elwood JM, Elwood JH. *Epidemiology of anencephalus and spina bifida*. Oxford: Oxford University Press, 1980.

Eurocat Central Registry, Belgium. Chorionic villus sampling and limb reduction. *EUROCAT Newsletter* 1992; 6(2).

Firth HV, Boyd PA, Chamberlain P, Mackenzie IZ, Lindenbaum RH, Huson SM. Severe limb abnormalities after chorionic villus sampling at 56-66 days' gestation. *Lancet* 1991; 337: 762-3.

Froster-Iskenius UG, Baird PA. Limb reduction defects in over one million consecutive livebirths. *Teratology* 1989; 39: 127-35.

Froster UG. Academicians are more likely to share each other's toothbrush than each other's nomenclature [Cohen, 1982]. *Am J Med Genet* 1996; 66: 471-4.

Froster UG, Baird PA. Congenital defects of the limbs in stillbirths: data from a population-based study. *Am J Med Genet* 1993; 46: 479-82.

Goldberg CS, Schwartz EM, Brunberg JA et al. Neurodevelopmental outcome of patients after the Fontan operation: A comparison between children with hypoplastic left heart syndrome and other functional single ventricle lesions. *J Pediatr* 2000; 137: 646-52.

Gorlin RJ, Cohen MM, Levin LS. Orofacial clefting syndromes: general aspects. In: *Syndromes of the Head and Neck*, 3rd Edition. New York: Oxford University Press, 1990: chapter 20, 693-700.

Goujard J. *Comparison of Changes in Neural Tube Defects (NTDs) Prevalence in Relation to Primary Prevention Strategies: Public Health Policy-Making and Implementation. Final Report*. 2001.

Graves CG, Matanoski GM, Tardiff RG. Weight of evidence for an association between adverse reproductive effects and exposure to disinfection by-products: a critical review. *Regul Toxicol Pharmacol* 2001; 2: 103-24.

Guibaud S, Robert E, Simplot A et al. Prenatal diagnosis of spina bifida after first-trimester valproate exposure. *Prenat Diagn* 1993; 13: 772.

Haddow JE. Commentary. Antenatal screening for Down syndrome: where are we and where next? *Lancet* 1998; 352: 336-7.

Hafner E, Steriste W, Scholler J et al. Prenatal diagnosis of fetal malformations. *Prenat Diagn* 1997; 17: 51-8.

Hall JG, Friedman JM, Kenna BA, Popkin J, Jawanda M, Arnold W. Clinical, genetic and epidemiological factors in neural tube defects. *Am J Hum Genet* 1988; 43: 827-37.

Hall JG, Solehdin F. Genetics of neural tube defects. *Men Retard Dev Disabil* 1999; 4: 269-81.

Harper PS. *Practical Genetic Counselling*, 5th Edition. Boston: Butterworth Heinemann, 1998.

Health Canada. *Canadian Perinatal Health Report, 2000*. Ottawa: Minister of Public Works and Government Services Canada, 2000.

Hennekens CH, Buring J. Statistical Association. In: Mayrent SL (Ed.), *Epidemiology in Medicine*. Toronto: Little, Brown and Company, 1987: 39-51.

Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol* 2001; 153: 961-8.

Honein MA, Paulozzi LJ, Erickson JD. Continued occurrence of Accutane-exposed pregnancies. *Teratology* 2001; 64: 142-7.

International Clearinghouse for Birth Defects Monitoring Systems. *Annual Report*. Rome, Italy, 2001.

Itikala PR, Watkins ML, Mulinare J, Moore CA, Liu Y. Maternal multivitamin use and orofacial clefts in offspring. *Teratology* 2001; 63: 79-86.

Jahoda MGJ, Brandenburg H, Cohen-Overbeek T et al. Terminal transverse limb defects and early chorionic villus sampling: evaluation of 4300 cases with completed follow-up. *Am J Med Genet* 1993; 43: 483-5.

James A. Letter to the Editor: Marine pollution and limb reduction defects. *Lancet* 1994; 343: 990-1.

James SJ, Pogribna M, Pogribny IP, Melnyk S, Hine RJ, Gibson JB, Yi P, Tafoya DL, Swenson DH, Wilson VL, Gaylor DW. Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. *Am J Clin Nutr* 1999; 70: 495-501.

Jones KL. Environmental Agents: Fetal Alcohol Syndrome. Fetal Hydantoin Syndrome. Fetal Trimethadione Syndrome. Retinoic Acid Embryopathy. In: *Smith's Recognizable Patterns of Human Development*, 5th Edition. Toronto: W.B. Saunders Company, 1997: 555-73.

Jones KL. *Smith's Recognizable Patterns of Human Malformation*, 4th Edition. Toronto: W.B. Saunders Company, 1988.

Jones KL. *Smith's Recognizable Patterns of Human Malformation*. 5th Edition. Toronto: W.B. Saunders Company, 1997.

Kallen B, Cocchi G, Knudsen LB et al. International study of sex ratio and twinning of neural tube defects. *Teratology* 1994; 50: 322-31.

Kallen B, Karlsson P, Lundell M, Wallgren A, Holm LE. Outcome of reproduction in women irradiated for hemangioma in infancy. *Radiat Res* 1998; 149: 202-8.

Kallen B, Rahmani TMZ, Winberg J. Infants with congenital limb reduction registered in the Swedish Register of Congenital Malformations. *Teratology* 1984; 29: 73-85.

Kallen K. Down's syndrome and maternal smoking in early pregnancy. *Genet Epidemiol* 1997; 14: 77-84.

Kallen K. Maternal smoking during pregnancy and limb reduction malformations in Sweden. *Am J Pub Health* 1997; 87: 29-32.

Kelsey JL. *Epidemiology of Musculoskeletal Disorders*. New York: Oxford University Press, 1982.

Kirke PN, Daly LE, Molloy A, Weir DG, Scott JM. Letter to Editor: Maternal folate status and risk of neural tube defects. *Lancet* 1996; 348: 67-8.

Kline J, Levin B, Kinney A, Stein Z, Susser M, Warburton D. Cigarette smoking and spontaneous abortion of known karyotype. Precise data but uncertain inferences. *Am J Epidemiol* 1995; 141: 417-27.

Last JM. *Dictionary of Epidemiology*. 2nd Edition. New York: Oxford University Press, 1988.

Lenz W. A short history of thalidomide embryopathy. *Teratology* 1988; 38: 203-15.

Leonard S, Bower C, Petterson B, Leonard H. Survival of infants born with Down's syndrome: 1980-1996. *Paediatr Perinat Epidemiol* 2000; 2: 163-71.

Lettieri J. Lips and Oral Cavity. In: Stevenson RE, Hall JG, Goodman RM (Eds.), *Human Malformations and Related Anomalies*. Vol. 2. New York: Oxford University Press, 1993: 367-81.

Lin AE, Herring AH, Amstutz KS et al. Cardiovascular Malformations: changes in prevalence and birth status, 1972-1990. *Am J Med Genet* 1999; 84: 102-10.

Loffredo CA, Silbergeld EK, Forenz C, Zhang J. Association of transposition of the great areteries in infants with maternal exposures to herbicides and rodenticides. *Am J Epidemiol* 2001; 153: 529-36.

Lowry RB, Renwick DHG. Incidence of cleft lip and palate in British Columbia Indians. *J Med Genet* 1969; 1: 67-9.

Lowry RB, Trimble BK. Incidence rates for cleft lip and palate in British Columbia 1952-71 for North American Indian, Japanese, Chinese and total populations: secular trends over twenty years. *Teratology* 1977; 3: 277-83.

March of Dimes Resource Center. *Birth Defects*. 1998. (Available: www.modimes.org).

McGuirk CK, Westgate M, Holmes LB. Limb deficiencies in newborn infants. *Pediatrics* 2001; 108: 1-7. (Available: www.pediatrics.org/cgi/content/full/108/4/e64).

Miller T, Stromland K. Teratogen update: Thalidomide: A review, with a focus on ocular findings and new potential uses. *Teratology* 1999; 60: 306-21.

Milunsky A. Maternal serum screening for neural tube and other defects. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 635-701.

Milunsky A. Multianalyte maternal serum screening for chromosome defects. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 702-49.

Milunsky A, Jick H, Jick SS et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. *JAMA* 1989; 262: 2847-52.

Milunsky A, Milunsky J. Genetic counseling: Preconception, prenatal and perinatal. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 1-3.

Montana E, Khoury MJ, Cragan JD, Sharma S, Dhar P, Fyfe D. Trends and outcomes after prenatal diagnosis of congenital cardiac malformations by fetal echocardiography in a well defined birth population, Atlanta, Georgia, 1990-1994. J *Am Coll Cardiol* 1996; 28: 1805-9.

Moore KL, Persaud TVN. *The Developing Human. Clinically Oriented Embryology*, 6th Edition. Toronto: W.B. Saunders Company, 1998.

Moore LL, Singer MR, Bradlee ML, Rothman KJ, Milunsky A. A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. *Epidemiology* 2000; 11: 689-94.

Mortality and Morbidity Weekly Report (MMWR). Recommendations and Reports. Chorionic villus sampling and amniocentesis: recommendations for prenatal counseling. 1995. (Available: www.cdc.gov/mmwr/preview/mmwrhtml/00038393.html).

Mossey PA, Little J. Epidemiology of oral clefts: an international perspective. In: *Cleft Lip and Palate. From Origin to Treatment*. Oxford University Press (in press, 2002).

Mulinare J, Cordero JF, Erickson JD, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. *JAMA* 1988; 206: 3141-5.

Myrianthopoulos NC, Melnick M. Studies in neural tube defects. I. Epidemiologic and etiologic aspects. *Am J Med Genet* 1987; 4: 738-96.

National Institute of Child Health and Human Development. *The National Children's Study*. 2002. (Available: http://nationalchildrensstudy.gov/about/overview.cfm).

Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. *N Eng J Med* 1984; 320: 19-23.

Olney RS et al. Letter to the Editor: Limb defects and gestational age at chorionic villus sampling. *Lancet* 1994; 344: 476.

Olshan AF, Schnitzer PG, Baird PA. Paternal age and the risk of congenital heart defects. *Teratology* 1994; 50: 80-4.

OMIM (Online Mendelian Inheritance of Man). *Conotruncal heart malformations*. Entry # 217095, 2001. (Available: www3.ncbi.nlm.nih.gov).

OMIM (Online Mendelian Inheritance of Man). *Down syndrome*. Entry #190685, 2001. (Available: www.3.ncbi.nlm.nih.gov).

OMIM (Online Mendelian Inheritance of Man). *Orofacial cleft*. Entry #19530, 2001. *Cleft palate*. Entry #119540, 2001. (Available: www3.ncbi.nlm.nih.gov).

O'Rahilly R, Muller F. *Human Embryology and Teratology*, 2nd Edition. Toronto: Wiley-Liss Publications, 1996.

Pilu F, Falco P, Perolo A, Visentin A. Ultrasound evaluation of the fetal neural axis. In: Callen PW (Ed.), *Ultrasonography in Obstetrics and Gynecology*, 4th Edition. New York: W.B. Saunders Company, 2000: 277-306.

Racial disparities in median age at death of persons with Down syndrome — United States, 1968-1997. *Morb Mortal Wkly Rep (MMWR)* 2001; 8: 463-5.

Reproductive Genetics Institute. *History of International Working Group on Preimplantation Genetics*, 2001. (Available: www.reproductivegenetics.com/history.shtml).

Reproductive Health Section, Health Canada. *National Folic Acid Campaign*. 2002. (Available: www.hc-sc.gc.ca/pphb-dgspsp/rhs-ssg/index.html).

Reprotox: An Information System on Environmental Hazards to Human Reproduction and Development. Alcohol, RTC 1127. 2001. (Available: http://reprotox.org/).

Reprotox: An Information System on Environmental Hazards to Human Reproduction and Development. Cigarette Smoking, RTC 1062. 2002. (Available: http://reprotox.org/dbtw-wpd/exec/dbtwpcgi.exe.).

Reprotox: An Information System on Environmental Hazards to Human Reproduction and Development. Thalidomide, RTC 2487; Misoprostol, RTC 2396; Methotrexate, RTC 1036; Aminopterin, RTC 3076. Isotretinoin, RTC 1098. 2001. (Available: http://reprotox.org/).

Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. Ambient air pollution and risk of birth defects in Southern California. *Am J Epidemiol* 2002; 155: 17-25.

Robert E, Guibaud P. Maternal valproic acid and congenital neural tube defects. *Lancet* 1982; 2: 937.

Rogers BT, Msall ME, Buck GM et al. Neurodevelopmental outcome of infants with hypoplastic left heart syndrome. *J Pediatr* 1995; 126: 496-8.

Roper EC, Konje JC, De Chazal RC et al. Genetic amniocentesis: gestation-specific pregnancy outcome and comparison of outcome following early and traditional amniocentesis. *Prenat Diagn* 1999; 19: 803-7.

Rosano A, Botto LD, Olney RS et al. Limb defects associated with major congenital anomalies: clinical and epidemiological study from the International Clearinghouse for Birth Defects Monitoring Systems. *Am J Med Genet* 2000; 93: 110-6.

Roumiana SB, Botton LD, Moore CA et al. Mortality associated with congenital heart defects in the United States. Trends and racial disparities, 1979-1997. *Circulation* 2000; 103: 2376-81.

Sanders DD, Stephens TD. Review of drug-induced limb defects in mammals. *Teratology* 1991; 44: 335-54.

Satomi G, Yasukochi S, Shimizu T et al. Has fetal echocardiography improved the prognosis of congenital heart disease? Comparison of patients with hypoplastic left heart syndrome with and without prenatal diagnosis. *Pediatr Int* 1999; 41: 728-32.

Sharland G, Rollings S, Simpson J, Anderson D. Letter to the Editor. Hypoplastic left heart syndrome. *Lancet* 2001; 357: 722.

Shashi V, Rickheim A, Pettenati MJ. Maternal homozygosity for the common MTHFR mutation as a potential risk factor for offspring with limb defects. *Am J Med Genet* 2001; 100: 25-9.

Shaw GM, Lammer EJ, Wasserman CR, O'Malley CD, Tolarova MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. *Lancet* 1995; 346: 393-6.

Shaw GM, O'Malley CD, Wasserman CR et al. Maternal periconceptional use of multivitamins and reduced risk for conotruncal heart and limb reduction defects among offspring. *Am J Med Genet* 1995; 59: 536-45.

Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect: Affected pregnancies among obese women. *JAMA* 1996; 275: 1093.

Shaw GM, Wasserman CR, Lammer EJ et al. Orofacial clefts, parental cigarette smoking, and transforming growth factor-alpha gene variants. *Am J Hum Genet* 1996; 58: 551-6.

Shaw GM, Wasserman CR, O'Malley CD, Nelson V, Jackson RJ. Maternal pesticide exposure from multiple sources and selected congenital anomalies. *Epidemiology* 1999; 10: 60-6.

Shprintzen RJ, Siegel-Sadewitz VL, Amato J et al. Anomalies associated with cleft lip, cleft palate, or both. *Am J Med Genet* 1985; 20: 585.

Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome. A meta-analysis. *JAMA* 2001; 285: 1044-55.

Snijders RJM, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10-14 weeks of gestation. *Lancet* 1998; 352: 343-6.

Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Genetic indications for prenatal diagnosis. *SOGC Journal* 2001; June: 105.

Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Guidelines for ultrasound as part of routine prenatal care. *SOGC Journal* 1999; August: 78. (Available: http://sogc.medical.org/SOGCnet/sogc_docs/common/guide/pdfs/ps78.pdf).

Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Techniques of prenatal diagnosis. 2001. (Available: http://sogc.medical.org/SOGCnet/sogc_docs/common/guide/pdfs/ps105.pdf).

Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical Practice Guidelines. Canadian Guidelines for Prenatal Diagnosis. Prenatal genetic screening for Down syndrome and open neural tube defects using maternal serum marker screening. *SOGC Journal* 1999; August: 79.

Society of Obstetricians and Gynaecologists of Canada. SOGC Policy Statement. Recommendations on the use of folic acid for the prevention of neural tube defects. *SOGC Journal* 1993; March Supplement: 41-6.

Sohan K, Freer M, Mercer N et al. Prenatal detection of facial clefts. *Fetal Diagn Ther* 2001; 4: 196-9.

Stevenson RE, Meyer LC. The limbs. In: Stevenson RE, Hall JG, Goodman RM (Eds.), *Human Malformations and Related Anomalies*. Vol. II. New York: Oxford University Press, 1993: 703-20.

Stevenson RE. The Genetic Basis of Human Anomalies. In: Stevenson RE, Hall JG, Goodman RM (Eds.), *Human Malformations and Related Anomalies*. Vol. 1. New York: Oxford University Press, 1993: 115.

Stoll C. Letter to the Editor. Classification of limb defects. *Am J Med Genet* 1998; 77: 439-41.

Stoll C, Alembik Y, Dott B, Roth MP. Study of Down syndrome in 238,942 consecutive births. *Ann Genet* 1998; 41: 44-51.

Stoll C, Garne E, Clementi M and EUROSCAN Study Group. Evaluation of prenatal diagnosis of associated congenital heart diseases by fetal ultrasonographic examination in Europe. *Prenat Diagn* 2001; 21: 243-52.

Stoll C, Wiesel A, Queisser-Luft A et al. Evaluation of the prenatal diagnosis of limb reduction deformities. EUROSCAN Study Group. *Prenat Diagn* 2000; 20: 811-8.

Tabor A, Madsen M, Obel EB et al. Randomized controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet* 1986; 8493: 1287-93.

Thalidomide Victims Association of Canada. 2002. (Available: www. thalidomide.ca/english/wit.html).

Tolarova M, Harris J. Reduced recurrence of orofacial clefts after periconceptional supplementation with high dose folic acid and multivitamins. *Teratology* 1995; 51: 71-8.

Tolmie J. Neural tube defects and other congenital malformations of the central nervous system. In: Emery A, Rimon D (Eds.), *Principles and Practice of Medical Genetics*, 3rd Edition. New York: Churchill Livingston, 1997: 2145-76.

Trasler JM, Doerksen T. Teratogen update: Paternal exposures-reproductive risks. *Teratology* 1999; 60: 161-72.

Van Allen MI, McCourt C, Lee NS. *Preconception health: folic acid for the primary prevention of neural tube defects. A resource document for health professionals, 2002*. Ottawa: Minister of Public Works and Government Services, Canada. 2002.

Van der Put NMJ, Eskes TKAB et al. Is the common 677-T mutation in the methylenetetrahydrofolate reductase gene a risk factor for neural tube defects? A meta-analysis. *Q J Med* 1997; 90: 111.

Villes YG, Nicolaides KH, Campbell S. Prenatal diagnosis of fetal malformations by ultrasound. In: Milunsky A (Ed.), *Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment*, 4th Edition. Baltimore: Johns Hopkins University Press, 1998: 750-812.

Vinceti M et al. Risk of birth defects in a population exposed to environmental lead pollution. *Sci Total Environ* 2001; 278: 23-30.

Vrijheid M et al. Chromosomal congenital anomalies and residence near hazardous waste landfill sites. *Lancet* 2002; 359: 320-2.

Wald NJ, Hackshaw AK. Combining ultrasound and biochemistry in first-trimester screening for Down's syndrome. *Prenat Diagn* 1997; 17: 821-9.

Wald NJ, Smith GL, Denesen JW, Petterson K. Serum screening for Down's syndrome between 8 and 14 weeks of pregnancy. *Br J Obstet Gynecol* 1996; 103: 407-12.

Wald N, Sneddon J, Densem J, Frost C, Stone R. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991; 338: 131-7.

Wald NJ, Watt HC, Hackshaw AK. Integrated screening for Down's syndrome on the basis of tests performed in the first and second trimesters. *N Engl J Med* 1999; 341: 461-7.

Waller DK, Mills JL, Simpson JL et al. Are obese women at higher risk for producing malformed offspring? *Am J Obstet Gynecol* 1994; 170: 541.

Wasserman CR, Shaw GM, O'Malley CD et al. Parental cigarette smoking and risk for congenital anomalies of the heart, neural tube, or limb. *Teratology* 1996; 53: 261-7.

Wen SW, Liu S, Joseph KS, Rouleau J, Allen A. Patterns of infant mortality caused by major congenital anomalies. *Teratology* 2000; 61: 342-6.

Wen SW, Liu S, Marcoux S, Fowler D. Uses and limitations of routine hospital admission/separation records for perinatal surveillance. *Chron Dis Can* 1997; 18: 113-9.

Wen SW, Rouleau J, Lowry RB et al. Congenital anomalies ascertained by two record systems run in parallel in the Canadian province of Alberta. *Can J Public Health* 2000; 91: 193-6.

Werler MM, Hayes C, Louik C et al. Multivitamin supplementation and risk of birth defects. *Am J Epidemiol* 1999; 150: 675-82.

Werler MM, Shapiro S, Mitchell AA. Periconceptional folic acid exposure and risk of occurrence of neural tube defects. *JAMA* 1993; 269: 1257-61.

Wertelecki W. International Birth Defects Information Systems: Special Thalidomide Edition. 1999. (Available: http://ibis-birthdefects.org/start/genothal.htm.).

WHO/PAHO Consultation on CVS. Evaluation of Chorionic villus sampling safety. *Prenat Diagn* 1999; 19: 97-9.

Wilson RD. Amniocentesis and chorionic villus sampling. *Curr Opin Obstet Gynecol* 2000; 12: 81-6.

Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Ann Neurol* 1985; 17: 278-82.

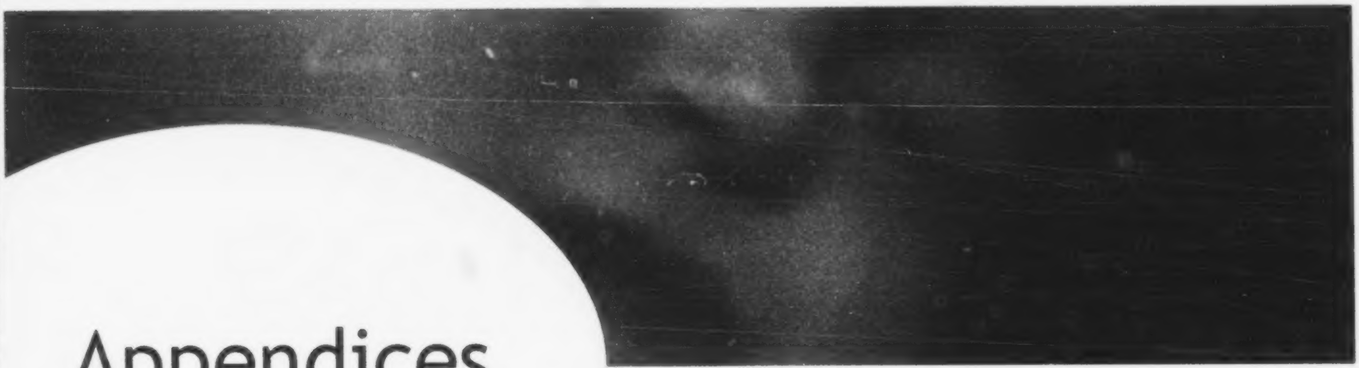
Wolfberg AJ, Nagey DA. Thyroid disease during pregnancy and subsequent congenital anomalies, Abstract #274. Society for Maternal-Fetal Medicine Annual Meeting, New Orleans, 2002.

Wright MJ, Newell JN, Charlton ME et al. Limb reduction defects in the northern region of England 1985-1992. *J of Epidemiol and Com Health* 1995; 49: 305-8.

Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. *Lancet* 2002; 359: 1019-25.

Yoon G, Chernos J, Sibbald B et al. Association between congenital foot anomalies and gestational age at amniocentesis. *Prenat Diagn* 2001; 21: 1437-41.

Zipursky A, Peters M, Poon A. Megakaryoblastic leukemia and Down syndrome — A review. In: McCoy EE, Epstein CJ (Eds.), *Oncology and Immunology of Down syndrome*. New York: Alan R. Liss Publisher, 1987: 33-56.



Appendices

Appendix A

Data Sources and Methods

Data sources

Canadian Congenital Anomalies Surveillance System

The Canadian Congenital Anomalies Surveillance System (CCASS) is the only ongoing national congenital anomalies surveillance system in Canada and is managed by the Division of Health Surveillance and Epidemiology in the Centre for Healthy Human Development at Health Canada. CCASS was first established in 1966 and was a founding member of the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS).

CCASS data are collected from the following sources:

1. Canadian Institute for Health Information (CIHI)

The primary source of CCASS data is CIHI's Discharge Abstract Database (DAD). This electronic database captures hospital separations (discharges, transfers and deaths) from the majority of Canada's acute care hospitals. The DAD contains considerable data on each hospitalization including demographic and residence information, length of stay, the most responsible diagnosis, and secondary and co-morbid diagnoses. The diagnoses are all coded according to the International Classification of Diseases, Ninth Revision (ICD-9).

2. Manitoba Health's Perinatal Hospitalization Database

3. Québec's Système de maintenance et d'exploitation des données pour l'étude de la clientèle hospitalière (Med-Écho)

Hospital separation data, similar to CIHI's DAD data, are submitted directly to CCASS from Manitoba and Québec. A detailed description of the hospitalization data sources are outlined in the *Canadian Perinatal Health Report, 2000.*[1]

4. Alberta Congenital Anomalies Surveillance System (ACASS)

ACASS is a surveillance system for congenital anomalies in the province of Alberta. The primary data sources for ACASS are vital statistics, hospital reporting and special communication with genetics clinics, specialty paediatric clinics and laboratories. Data from ACASS are sent first to Alberta Health/Vital Statistics and then forwarded to CCASS.

Strengths and limitations of CCASS

CCASS covers approximately 345,000 total births each year and is able to report birth prevalence rates for 15 summary categories and 57 specific categories of congenital anomalies. CCASS is capable of calculating rates at the national, provincial and, for some provinces, census and census subdivision levels. CCASS can also produce statistical comparisons of birth prevalence between jurisdictions.

As CCASS obtains data primarily from large hospitalization databases, several limitations do exist. First, the system relies on hospitalization records and ICD-9 codes. Codes and diagnoses are not confirmed once they are abstracted from the hospital record. Furthermore, important limitations in the ICD-9 coding system with regard to congenital anomalies have been identified. Reliance on hospitalization records also results in a failure to capture anomalies that are diagnosed on an outpatient basis. Second, for most jurisdictions, only anomalies affecting stillbirths and live births are captured. Therefore, affected fetuses that do not meet the criteria for stillbirths (a birth weight of greater than or equal to 500 grams, or greater than or equal to 20 weeks in pregnancy, in most provinces) are not captured in the system. Consequently, most prenatally diagnosed anomalies that result in terminations of pregnancy are not included in CCASS. Third, CCASS records do not include maternal exposure and behavioural risk factor information. Finally, the timeliness of CCASS data is less than ideal. As live births up to 1 year of age are ascertained by CCASS, delays of greater than two years can exist in reporting. As well as these general limitations, individual data sources have their own limitations. For example, the Med-Écho system in Québec may not capture all stillbirths that occur outside of the province.

Limitations also exist in the processing of data once received by CCASS. Hospitalization data may include multiple admissions for the same infant, and data received from the DAD do not contain identifying variables. As a result, a melding process is used to remove duplicate admissions using variables such as birth date, scrambled health insurance number, etc. The accuracy and completeness of these variables can vary and created inflated rates for some areas.

The quality of CCASS data has been formally evaluated on two fronts. First, an evaluation of CIHI's DAD examined several perinatal outcomes, including some congenital anomalies. The evaluation concluded that major diagnoses were well captured, but the more complex or obscure diagnoses were less reliably coded.[2] This conclusion was further supported in a recent study comparing Alberta congenital anomalies data derived from CCASS versus rates derived from the active, multiple-source ascertainment system of ACASS. The study reported good agreement between CCASS and ACASS for obvious anomalies, such as anencephaly. However, for less clear-cut diagnoses, such as lung agenesis, the agreement was poor. The specific anomalies presented in this report demonstrated fair to good agreement in the validation study.

Methods

CCASS provides the Canadian and provincial/territorial birth prevalence for specific congenital anomalies. The statistical methods used for this report were primarily descriptive. Where events were rare or rates were based on a small sample, caution should be exercised in interpreting results.

Statistics presented consist of:

1. Birth Prevalence — The birth prevalence for specific congenital anomalies or categories of congenital anomalies were calculated using the number of stillbirths or live births with an ICD-9 code(s) for a specific congenital anomaly as the numerator and the total number of births (live births and stillbirths) as the denominator. The birth prevalence for selected congenital anomalies are presented per 10,000 total births.

2. Temporal Trends at the National Level — The time period covered in the temporal trends dates back to 1989. If complete provincial data were not available for all years, such as the case with Nova Scotia, data from the province were excluded from the Canadian rates. Statistical tests of trend were performed to identify statistically significant trends in the birth prevalence of specific congenital anomalies over time.

3. Interprovincial/Territorial Comparisons — Interprovincial/territorial comparisons of birth prevalence for specific congenital anomalies are presented for the combined three-year period, 1997-1999. For all provincial/territorial rates, 95% confidence intervals (CIs) were calculated to allow an accurate comparison of provincial/territorial rates. Separate statistics could not be calculated for Nunavut as the time period covered in this report preceded the creation of this new territory.

4. International Comparisons — International data were obtained from the ICBDMS *Annual Report*, 2001.[3] The international comparisons were descriptive in presentation, as there are critical differences in definitions, inclusion and exclusion criteria, and in the methods of ascertainment of congenital anomalies among the international programs.

The majority of data are presented graphically. However, data tables corresponding to all figures are presented in Appendix D.

References

1. Health Canada. *Canadian Perinatal Health Report, 2000*. Ottawa: Minister of Public Works and Government Services Canada, 2000: 89-93.
2. Wen SW, Rouleau J, Lowry RB et al. Congenital anomalies ascertained by two record systems run parallel in the Canadian province of Alberta. *Can J Public Health* 2000; 91: 193-6.
3. International Clearinghouse for Birth Defects Monitoring Systems. *Annual Report*. Rome, Italy, 2001.

Appendix B

ICD-9 Codes for Congenital Anomalies Listed in this Report

Categories	ICD-9 Code
Down syndrome	758.0
Neural tube defects	740.0-740.2, 741.0-741.9, 742.0
Anencephaly and similar anomalies	740.0-740.2
Spina bifida	741.0-741.9
Congenital heart defects	745.0-745.9, 746.0-746.9
Hypoplastic left heart syndrome	746.7
Cleft palate	749.0
Cleft lip with or without cleft palate	749.1-749.2
Limb reduction defects	755.2-755.4

Appendix C

List of Acronyms

ACASS	Alberta Congenital Anomalies Surveillance System
CCASN	Canadian Congenital Anomalies Surveillance Network
CCASS	Canadian Congenital Anomalies Surveillance System
CHD(s)	congenital heart defect(s)
CI	confidence interval
CIHI	Canadian Institute for Health Information
CL/P	cleft lip with or without cleft palate
CP	cleft palate
CSC	Centre for Surveillance Coordination
CVS	chorionic villus sampling
DAD	Discharge Abstract Database
DS	Down syndrome
E3	unconjugated estriol
FAS	fetal alcohol syndrome
FMF	Fetal Medicine Foundation (England)
hCG	human chorionic gonadotropin
HLHS	hypoplastic left heart syndrome
HSR	Health Status Registry
ICBDMS	International Clearinghouse for Birth Defects Monitoring Systems
ICD-9	International Classification of Diseases, Ninth Revision
IPS	integrated prenatal screening
LRD(s)	limb reduction defect(s)
Med-Écho	Système de maintenance et d'exploitation des données pour l'étude de la clientèle hospitalière
MSAFP	maternal serum alpha fetoprotein
MSS	maternal serum screening
MTHFR	methylene tetrahydrofolate reductase
NSAPD	Nova Scotia Atlee Perinatal Database
NT	nuchal translucency
NTD(s)	neural tube defect(s)
PGD	preimplantation genetic diagnosis
SOGC	Society of Obstetricians and Gynaecologists of Canada
TOP	terminations of pregnancy
WHO	World Health Organization

Appendix D

List of Data Tables

Table D1.1:
Down syndrome (DS) rate, Canada (excluding Nova Scotia), 1989-1999 61

Table D1.2:
Down syndrome (DS) rate, by province/territory, Canada, 1997-1999 61

Table D2.1:
Neural tube defect (NTD) rate, Canada (excluding Nova Scotia), 1989-1999 62

Table D2.2:
Spina bifida rate, Canada (excluding Nova Scotia), 1989-1999 62

Table D2.3:
Anencephaly rate, Canada (excluding Nova Scotia), 1989-1999 63

Table D2.4:
Neural tube defect (NTD) rate, by province/territory, Canada, 1997-1999 63

Table D2.5:
Spina bifida rate, by province/territory, Canada, 1997-1999 64

Table D2.6:
Anencephaly rate, by province/territory, Canada, 1997-1999 64

Table D3.1:
Congenital heart defect (CHD) rate, Canada (excluding Nova Scotia), 1989-1999 65

Table D3.2:
Hypoplastic left heart syndrome (HLHS) rate, Canada (excluding Nova Scotia), 1989-1999 65

Table D3.3:
Hypoplastic left heart syndrome (HLHS) rate, by province/territory, Canada, 1997-1999 66

Table D4.1:
Cleft lip with/without cleft palate (CL/P) and cleft palate (CP) rates, Canada (excluding Nova Scotia), 1989-1999 66

Table D4.2:
Cleft lip with or without cleft palate (CL/P) rate, by province/territory, Canada, 1997-1999 67

Table D4.3:
Cleft palate (CP) rate, by province/territory, Canada, 1997-1999 67

Table D5.1:
Limb reduction defect (LRD) rate, Canada (excluding Nova Scotia), 1989-1999 68

Table D5.2:
Limb reduction defect (LRD) rate, by province/territory, Canada, 1997-1999 68

61 - 62

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

Micromedia
ProQuest

20 Victoria Street
Toronto, Ontario M5C 2N8
Tel.: (416) 362-5211
Toll Free: 1-800-387-2689
Fax: (416) 362-6161
Email: info@micromedia.on.ca

Data Tables

Table D1.1

Down syndrome (DS) rate,

Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	454	12.1
1990	390,839	567	14.5
1991	389,926	556	14.3
1992	384,740	460	12.0
1993	377,167	490	13.0
1994	375,451	461	12.3
1995	368,100	493	13.4
1996	356,188	430	12.1
1997	341,122	468	13.7
1998	334,133	458	13.7
1999	328,493	466	14.2

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D1.2

Down syndrome (DS) rate, by province/territory, *Canada, 1997-1999*

Province/territory	Total births	Proportion of hospital deliveries by women aged 35 years or older (%)*	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	10.1	20	12.9	(7.8-19.9)
Prince Edward Island	4,550	13.7	8	17.6	(7.6-34.6)
Nova Scotia	29,346	12.9	59	20.1	(15.3-25.9)
New Brunswick	24,017	9.1	43	17.9	(12.9-24.1)
Québec	225,053	N/A	298	13.2	(11.8-14.8)
Ontario	406,064	17.6	553	13.6	(12.5-14.8)
Manitoba	43,232	14.0	59	13.6	(10.4-17.6)
Saskatchewan	37,957	10.7	61	16.1	(12.3-20.6)
Alberta	113,844	14.1	124	10.9	(9.0-13.0)
British Columbia	129,230	18.1	218	16.9	(14.7-19.3)
Yukon	1,213	20.7	3	24.7	(5.0-72.3)
Northwest Territories	3,050	11.7	5	16.4	(5.3-38.2)
CANADA	**1,033,094**	**16.1**	**1,451**	**14.0**	**(13.3-14.8)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*1999-2000 data. (Source: Canadian Institute for Health Information. Discharge Abstract Database, 1999-2000.)

CI – confidence interval.

Table D1.1

Down syndrome (DS) rate,

Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	454	12.1
1990	390,839	567	14.5
1991	389,926	556	14.3
1992	384,740	460	12.0
1993	377,167	490	13.0
1994	375,451	461	12.3
1995	368,100	493	13.4
1996	356,188	430	12.1
1997	341,122	468	13.7
1998	334,133	458	13.7
1999	328,493	466	14.2

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D1.2

Down syndrome (DS) rate, by province/territory, *Canada, 1997-1999*

Province/territory	Total births	Proportion of hospital deliveries by women aged 35 years or older (%)*	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	10.1	20	12.9	(7.8-19.9)
Prince Edward Island	4,550	13.7	8	17.6	(7.6-34.6)
Nova Scotia	29,346	12.9	59	20.1	(15.3-25.9)
New Brunswick	24,017	9.1	43	17.9	(12.9-24.1)
Quebec	225,053	N/A	298	13.2	(11.8-14.8)
Ontario	406,064	17.6	553	13.6	(12.5-14.8)
Manitoba	43,232	14.0	59	13.6	(10.4-17.6)
Saskatchewan	37,957	10.7	61	16.1	(12.3-20.6)
Alberta	113,844	14.1	124	10.9	(9.0-13.0)
British Columbia	129,230	18.1	218	16.9	(14.7-19.3)
Yukon	1,213	20.7	3	24.7	(5.0-72.3)
Northwest Territories	3,050	11.7	5	16.4	(5.3-38.2)
CANADA	**1,033,094**	**16.1**	**1,451**	**14.0**	**(13.3-14.8)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*1999-2000 data. (Source: Canadian Institute for Health Information. Discharge Abstract Database, 1999-2000.)

CI – confidence interval.

Table D2.1

Neural tube defect (NTD) rate,
Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	416	11.1
1990	390,839	430	11.0
1991	389,926	389	10.0
1992	384,740	370	9.6
1993	377,167	345	9.1
1994	375,451	349	9.3
1995	368,100	340	9.2
1996	356,188	257	7.2
1997	341,122	257	7.5
1998	334,133	188	5.6
1999	328,493	185	5.6

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D2.2

Spina bifida rate, *Canada (excluding Nova Scotia),* 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	299	8.0
1990	390,839	310	7.9
1991	389,926	268	6.9
1992	384,740	265	6.9
1993	377,167	239	6.3
1994	375,451	237	6.3
1995	368,100	238	6.5
1996	356,188	184	5.2
1997	341,122	182	5.3
1998	334,133	138	4.1
1999	328,493	130	4.0

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D2.3

Anencephaly rate, *Canada (excluding Nova Scotia),* 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	81	2.2
1990	390,839	87	2.2
1991	389,926	75	1.9
1992	384,740	63	1.6
1993	377,167	72	1.9
1994	375,451	68	1.8
1995	368,100	65	1.8
1996	356,188	40	1.1
1997	341,122	51	1.5
1998	334,133	30	0.9
1999	328,493	31	0.9

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D2.4

Neural tube defect (NTD) rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	15	9.7	(5.4-15.9)
Prince Edward Island	4,550	0	0.0	(0.0-8.1)
Nova Scotia	29,346	28	9.5	(6.3-13.8)
New Brunswick	24,017	19	7.9	(4.8-12.3)
Québec	225,053	121	5.4	(4.5-6.4)
Ontario	406,064	265	6.5	(5.8-7.4)
Manitoba	43,232	36	8.3	(5.8-11.5)
Saskatchewan	37,957	22	5.8	(3.6-8.8)
Alberta	113,844	52	4.6	(3.4-6.0)
British Columbia	129,230	100	7.7	(6.3-9.4)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	0	0.0	(0.0-12.0)
CANADA	**1,033,094**	**658**	**6.4**	**(5.9-6.9)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI – confidence interval.

Table D2.1

Neural tube defect (NTD) rate,

Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	416	11.1
1990	390,839	430	11.0
1991	389,926	389	10.0
1992	384,740	370	9.6
1993	377,167	345	9.1
1994	375,451	349	9.3
1995	368,100	340	9.2
1996	356,188	257	7.2
1997	341,122	257	7.5
1998	334,133	188	5.6
1999	328,493	185	5.6

Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D2.2

Spina bifida rate, *Canada (excluding Nova Scotia),* 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	299	8.0
1990	390,839	310	7.9
1991	389,926	268	6.9
1992	384,740	265	6.9
1993	377,167	239	6.3
1994	375,451	237	6.3
1995	368,100	238	6.5
1996	356,188	184	5.2
1997	341,122	182	5.3
1998	334,133	138	4.1
1999	328,493	130	4.0

Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D2.3

Anencephaly rate, *Canada (excluding Nova Scotia),* 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	81	2.2
1990	390,839	87	2.2
1991	389,926	75	1.9
1992	384,740	63	1.6
1993	377,167	72	1.9
1994	375,451	68	1.8
1995	368,100	65	1.8
1996	356,188	40	1.1
1997	341,122	51	1.5
1998	334,133	30	0.9
1999	328,493	31	0.9

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D2.4

Neural tube defect (NTD) rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	15	9.7	(5.4-15.9)
Prince Edward Island	4,550	0	0.0	(0.0-8.1)
Nova Scotia	29,346	28	9.5	(6.3-13.8)
New Brunswick	24,017	19	7.9	(4.8-12.3)
Quebec	225,053	121	5.4	(4.5-6.4)
Ontario	406,064	265	6.5	(5.8-7.4)
Manitoba	43,232	36	8.3	(5.8-11.5)
Saskatchewan	37,957	22	5.8	(3.6-8.8)
Alberta	113,844	52	4.6	(3.4-6.0)
British Columbia	129,230	100	7.7	(6.3-9.4)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	0	0.0	(0.0-12.0)
CANADA	**1,033,094**	**658**	**6.4**	**(5.9-6.9)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI confidence interval.

Table D2.5

Spina bifida rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	9	5.8	(2.6-11.0)
Prince Edward Island	4,550	0	0.0	(0.0-8.0)
Nova Scotia	29,346	18	6.1	(3.6-9.7)
New Brunswick	24,017	14	5.8	(3.2-9.8)
Québec	225,053	86	3.8	(3.0-4.7)
Ontario	406,064	190	4.7	(4.0-5.4)
Manitoba	43,232	24	5.6	(3.5-8.3)
Saskatchewan	37,957	17	4.5	(2.6-7.2)
Alberta	113,844	34	3.0	(2.1-4.2)
British Columbia	129,230	76	5.9	(4.6-7.4)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	0	0.0	(0.0-12.0)
CANADA	**1,033,094**	**468**	**4.5**	**(4.1-4.9)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI – confidence interval.

Table D2.6

Anencephaly rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	3	1.9	(0.4-5.6)
Prince Edward Island	4,550	0	0.0	(0.0-8.1)
Nova Scotia	29,346	4	1.4	(0.4-3.5)
New Brunswick	24,017	2	0.8	(0.1-3.0)
Québec	225,053	14	0.6	(0.3-1.0)
Ontario	406,064	52	1.3	(0.9-1.7)
Manitoba	43,232	7	1.6	(0.6-3.3)
Saskatchewan	37,957	3	0.8	(0.1-2.3)
Alberta	113,844	13	1.1	(0.6-1.9)
British Columbia	129,230	18	1.4	(0.8-2.2)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	0	0.0	(0.0-12.0)
CANADA	**1,033,094**	**116**	**1.1**	**(0.9-1.3)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI – confidence interval.

Table D3.1

Congenital heart defect (CHD) rate,

Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	3,065	81.6
1990	390,839	3,448	88.2
1991	389,926	3,518	90.2
1992	384,740	3,337	86.7
1993	377,167	3,362	89.1
1994	375,451	3,167	84.4
1995	368,100	3,377	91.7
1996	356,188	3,471	97.4
1997	341,122	3,484	102.1
1998	334,133	3,536	105.8
1999	328,493	3,407	103.7

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D3.2

Hypoplastic left heart syndrome (HLHS) rate,

Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	108	2.9
1990	390,839	133	3.4
1991	389,926	110	2.8
1992	384,740	127	3.3
1993	377,167	82	2.2
1994	375,451	96	2.6
1995	368,100	123	3.3
1996	356,188	91	2.6
1997	341,122	85	2.5
1998	334,133	96	2.9
1999	328,493	89	2.7

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D2.5

Spina bifida rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	9	5.8	(2.6-11.0)
Prince Edward Island	4,550	0	0.0	(0.0-8.0)
Nova Scotia	29,346	18	6.1	(3.6-9.7)
New Brunswick	24,017	14	5.8	(3.2-9.8)
Quebec	225,053	86	3.8	(3.0-4.7)
Ontario	406,064	190	4.7	(4.0-5.4)
Manitoba	43,232	24	5.6	(3.5-8.3)
Saskatchewan	37,957	17	4.5	(2.6-7.2)
Alberta	113,844	34	3.0	(2.1-4.2)
British Columbia	129,230	76	5.9	(4.6-7.4)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	0	0.0	(0.0-12.0)
CANADA	**1,033,094**	**468**	**4.5**	**(4.1-4.9)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.
*Combined rate for the three-year period 1997-1999.
CI = confidence interval.

Table D2.6

Anencephaly rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	3	1.9	(0.4-5.6)
Prince Edward Island	4,550	0	0.0	(0.0-8.1)
Nova Scotia	29,346	4	1.4	(0.4-3.5)
New Brunswick	24,017	2	0.8	(0.1-3.0)
Quebec	225,053	14	0.6	(0.3-1.0)
Ontario	406,064	52	1.3	(0.9-1.7)
Manitoba	43,232	7	1.6	(0.6-3.3)
Saskatchewan	37,957	3	0.8	(0.1-2.3)
Alberta	113,844	13	1.1	(0.6-1.9)
British Columbia	129,230	18	1.4	(0.8-2.2)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	0	0.0	(0.0-12.0)
CANADA	**1,033,094**	**116**	**1.1**	**(0.9-1.3)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.
*Combined rate for the three-year period 1997-1999.
CI = confidence interval.

Table D3.1

Congenital heart defect (CHD) rate,

Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	3,065	81.6
1990	390,839	3,448	88.2
1991	389,926	3,518	90.2
1992	384,740	3,337	86.7
1993	377,167	3,362	89.1
1994	375,451	3,167	84.4
1995	368,100	3,377	91.7
1996	356,188	3,471	97.4
1997	341,122	3,484	102.1
1998	334,133	3,536	105.8
1999	328,493	3,407	103.7

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D3.2

Hypoplastic left heart syndrome (HLHS) rate,

Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	108	2.9
1990	390,839	133	3.4
1991	389,926	110	2.8
1992	384,740	127	3.3
1993	377,167	82	2.2
1994	375,451	96	2.6
1995	368,100	123	3.3
1996	356,188	91	2.6
1997	341,122	85	2.5
1998	334,133	96	2.9
1999	328,493	89	2.7

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D3.3

Hypoplastic left heart syndrome (HLHS) rate, by province/territory,

*Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	4	2.6	(0.7-6.6)
Prince Edward Island	4,550	0	0.0	(0.0-8.1)
Nova Scotia	29,346	20	6.8	(4.2-10.5)
New Brunswick	24,017	0	0.0	(0.0-1.5)
Québec	225,053	80	3.6	(2.8 -4.4)
Ontario	406,064	98	2.4	(1.9-2.9)
Manitoba	43,232	12	2.8	(1.4-4.8)
Saskatchewan	37,957	14	3.7	(2.0-6.2)
Alberta	113,844	34	3.0	(2.1-4.2)
British Columbia	129,230	28	2.2	(1.4-3.1)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	0	0.0	(0.0-12.0)
CANADA	**1,033,094**	**290**	**2.8**	**(2.5-3.1)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI – confidence interval.

Table D4.1

Cleft lip with/without cleft palate (CL/P) and cleft palate (C/P) rates,

Canada (excluding Nova Scotia), 1989-1999*

		Cleft lip with/without cleft palate (CL/P)		Cleft palate (C/P)	
Year	Total births	Number of cases	Prevalence rate per 10,000 total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	399	10.6	252	6.7
1990	390,839	480	12.3	290	7.4
1991	389,926	453	11.6	291	7.5
1992	384,740	468	12.2	268	7.0
1993	377,167	394	10.4	266	7.1
1994	375,451	388	10.3	261	7.0
1995	368,100	411	11.2	230	6.2
1996	356,188	396	11.1	269	7.6
1997	341,122	361	10.6	267	7.8
1998	334,133	350	10.5	246	7.4
1999	328,493	356	10.8	249	7.6

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D4.2

Cleft lip with or without cleft palate (CL/P) rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	32	20.6	(14.1-29.8)
Prince Edward Island	4,550	3	6.6	(1.3-19.3)
Nova Scotia	29,346	43	14.7	(10.6-19.7)
New Brunswick	24,017	14	5.8	(3.2-9.8)
Québec	225,053	200	8.9	(7.7-10.2)
Ontario	406,064	358	8.8	(7.9-9.8)
Manitoba	43,232	62	14.3	(11.0-18.4)
Saskatchewan	37,957	56	14.8	(11.1-19.1)
Alberta	113,844	106	9.3	(7.6-11.3)
British Columbia	129,230	230	17.8	(15.6-20.2)
Yukon	1,213	0	0	(0.0-30.2)
Northwest Territories	3,050	6	19.7	(7.2-42.8)
CANADA	**1,033,094**	**1,110**	**10.7**	**(10.1-11.4)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI – confidence interval.

Table D4.3

Cleft palate (CP) rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	9	5.8	(2.6-11.0)
Prince Edward Island	4,550	3	6.6	(1.3-19.3)
Nova Scotia	29,346	32	10.9	(7.4-15.4)
New Brunswick	24,017	30	12.5	(8.4-17.8)
Québec	225,053	192	8.5	(7.4-9.8)
Ontario	406,064	258	6.4	(5.6-7.2)
Manitoba	43,232	39	9.0	(6.4-12.3)
Saskatchewan	37,957	25	6.6	(4.3-9.7)
Alberta	113,844	95	8.3	(6.7-10.2)
British Columbia	129,230	110	8.5	(7.0-10.2)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	1	3.3	(0.0-18.2)
CANADA	**1,033,094**	**794**	**7.7**	**(7.2-8.2)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI – confidence interval.

Table D3.3

Hypoplastic left heart syndrome (HLHS) rate, by province/territory,
*Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	4	2.6	(0.7-6.6)
Prince Edward Island	4,550	0	0.0	(0.0-8.1)
Nova Scotia	29,346	20	6.8	(4.2-10.5)
New Brunswick	24,017	0	0.0	(0.0-1.5)
Quebec	225,053	80	3.6	(2.8 -4.4)
Ontario	406,064	98	2.4	(1.9-2.9)
Manitoba	43,232	12	2.8	(1.4-4.8)
Saskatchewan	37,957	14	3.7	(2.0-6.2)
Alberta	113,844	34	3.0	(2.1-4.2)
British Columbia	129,230	28	2.2	(1.4-3.1)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	0	0.0	(0.0-12.0)
CANADA	**1,033,094**	**290**	**2.8**	**(2.5-3.1)**

Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI confidence interval.

Table D4.1

Cleft lip with/without cleft palate (CL/P) and cleft palate (C/P) rates,
Canada (excluding Nova Scotia), 1989-1999*

		Cleft lip with/without cleft palate (CL/P)		Cleft palate (C/P)	
Year	Total births	Number of cases	Prevalence rate per 10,000 total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	399	10.6	252	6.7
1990	390,839	480	12.3	290	7.4
1991	389,926	453	11.6	291	7.5
1992	384,740	468	12.2	268	7.0
1993	377,167	394	10.4	266	7.1
1994	375,451	388	10.3	261	7.0
1995	368,100	411	11.2	230	6.2
1996	356,188	396	11.1	269	7.6
1997	341,122	361	10.6	267	7.8
1998	334,133	350	10.5	246	7.4
1999	328,493	356	10.8	249	7.6

Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D4.2

Cleft lip with or without cleft palate (CL/P) rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	32	20.6	(14.1-29.8)
Prince Edward Island	4,550	3	6.6	(1.3-19.3)
Nova Scotia	29,346	43	14.7	(10.6-19.7)
New Brunswick	24,017	14	5.8	(3.2-9.8)
Quebec	225,053	200	8.9	(7.7-10.2)
Ontario	406,064	358	8.8	(7.9-9.8)
Manitoba	43,232	62	14.3	(11.0-18.4)
Saskatchewan	37,957	56	14.8	(11.1-19.1)
Alberta	113,844	106	9.3	(7.6-11.3)
British Columbia	129,230	230	17.8	(15.6-20.2)
Yukon	1,213	0	0	(0.0-30.2)
Northwest Territories	3,050	6	19.7	(7.2-42.8)
CANADA	**1,033,094**	1,110	**10.7**	**(10.1-11.4)**

Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI — confidence interval.

Table D4.3

Cleft palate (CP) rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	9	5.8	(2.6-11.0)
Prince Edward Island	4,550	3	6.6	(1.3-19.3)
Nova Scotia	29,346	32	10.9	(7.4-15.4)
New Brunswick	24,017	30	12.5	(8.4-17.8)
Quebec	225,053	192	8.5	(7.4-9.8)
Ontario	406,064	258	6.4	(5.6-7.2)
Manitoba	43,232	39	9.0	(6.4-12.3)
Saskatchewan	37,957	25	6.6	(4.3-9.7)
Alberta	113,844	95	8.3	(6.7-10.2)
British Columbia	129,230	110	8.5	(7.0-10.2)
Yukon	1,213	0	0.0	(0.0-30.2)
Northwest Territories	3,050	1	3.3	(0.0-18.2)
CANADA	**1,033,094**	794	**7.7**	**(7.2-8.2)**

Source: Health Canada, Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI — confidence interval.

Table D5.1

Limb reduction defect (LRD) rate,
Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	179	4.8
1990	390,839	173	4.4
1991	389,926	203	5.2
1992	384,740	188	4.9
1993	377,167	168	4.5
1994	375,451	160	4.3
1995	368,100	161	4.4
1996	356,188	159	4.5
1997	341,122	121	3.5
1998	334,133	151	4.5
1999	328,493	120	3.7

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D5.2

Limb reduction defect (LRD) rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	3	1.9	(0.4-5.6)
Prince Edward Island	4,550	0	0.0	(0.0-8.1)
Nova Scotia	29,346	18	6.1	(3.6-9.7)
New Brunswick	24,017	4	1.7	(0.4-4.3)
Quebec	225,053	112	5.0	(4.1-6.0)
Ontario	406,064	121	3.0	(2.5-3.6)
Manitoba	43,232	20	4.6	(2.8-7.1)
Saskatchewan	37,957	25	6.6	(4.3-9.7)
Alberta	113,844	50	4.4	(3.2-5.8)
British Columbia	129,230	55	4.3	(3.2-5.5)
Yukon	1,213	1	8.2	(0.1-45.9)
Northwest Territories	3,050	1	3.3	(0.1-18.2)
CANADA	1,033,094	410	4.0	(3.6-4.4)

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI — confidence interval.

Table D5.1

Limb reduction defect (LRD) rate,

Canada (excluding Nova Scotia), 1989-1999*

Year	Total births	Number of cases	Prevalence rate per 10,000 total births
1989	375,840	179	4.8
1990	390,839	173	4.4
1991	389,926	203	5.2
1992	384,740	188	4.9
1993	377,167	168	4.5
1994	375,451	160	4.3
1995	368,100	161	4.4
1996	356,188	159	4.5
1997	341,122	121	3.5
1998	334,133	151	4.5
1999	328,493	120	3.7

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1989-1999.

*Nova Scotia is excluded because data are not available for all years.

Table D5.2

Limb reduction defect (LRD) rate, by province/territory, *Canada, 1997-1999**

Province/territory	Total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births	
Newfoundland	15,538	3	1.9	(0.4-5.6)
Prince Edward Island	4,550	0	0.0	(0.0-8.1)
Nova Scotia	29,346	18	6.1	(3.6-9.7)
New Brunswick	24,017	4	1.7	(0.4-4.3)
Québec	225,053	112	5.0	(4.1-6.0)
Ontario	406,064	121	3.0	(2.5-3.6)
Manitoba	43,232	20	4.6	(2.8-7.1)
Saskatchewan	37,957	25	6.6	(4.3-9.7)
Alberta	113,844	50	4.4	(3.2-5.8)
British Columbia	129,230	55	4.3	(3.2-5.5)
Yukon	1,213	1	8.2	(0.1-45.9)
Northwest Territories	3,050	1	3.3	(0.1-18.2)
CANADA	**1,033,094**	410	**4.0**	**(3.6-4.4)**

Source: Health Canada. Canadian Congenital Anomalies Surveillance System, 1997-1999.

*Combined rate for the three-year period 1997-1999.

CI – confidence interval.

Canadian
Perinatal
Surveillance System

Congenital Anomalies in Canada

A Perinatal Health Report, 2002